Influenza Mortality and Hospital Admissions for Influenza, Pneumonia, Emphysema and Bronchitis During the Influenza Epidemic 1989-90: Case-Control Study of Risk-factors and Effectiveness of Influenza Vaccine.

BY

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To my family ..... past, present, and future.

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Abbreviations used in the thesis

AIDS	acquired immunodeficiency syndrome.
CI	confidence interval.
CMO	Chief Medical Officer
COPD	chronic obstructive pulmonary disease.
DF	degree of freedom.
DHAs	District Health Authorities.
DoH	Department of Health.
FHSAs	Family Health Services Authorities.
GP	general practitioner.
HA	haemagglutinin.
HI	haemagglutination inhibition.
HIV	human immunodeficiency virus.
ICD	International classification of diseases.
IL	Interleukin.
LRECs	local research ethics committee.
MEFR	Maximum expiratory flow rate.
NA	neuraminidase.
OPCS	Office of Population Censuses and Surveys.
PEFR	peak expiratory flow rate.
PHLS	Public Health Laboratory Service.
RCP	Royal College of Physicians.
UK	United Kingdom.
US	United States.
VE	vaccine effectiveness.
WHO	World Health Organisation.

Declaration of the work done by the author

The protocol for these studies was written prior to my appointment in Leicester, however I devised the proforma to collect data for the mortality study, made the contacts with the Directors of Public Health and General Mangers of different Family Health Services Authorities (FHSAs). I also identified all chairmen of the local research ethics committees (LRECs), wrote to them and completed all application forms for ethical committee approval. I attended three of LREC meetings to present and discuss the proposal at their request.

I visited each District Health Authority involved in this study on at least three occasions. I identified all individuals whose primary or contributory cause of death was influenza by sifting through death records; reviewed all General Practitioners' records for cases and controls in each of 24 FHSAs.

The admission study was started prior to my arrival in Leicester by Dr Nicholson and the Public Health Medicine Senior House Officer at the time (Dr Goyder); 80 proformas for admissions were completed using information from hospital medical records. When I was appointed I completed proformas for the remaining 184 admissions (264 proformas were completed in total). I collated data on vaccination history for all 264 admissions by reviewing general practitioners' records. I devised the proforma for the collecting of data concerning the controls for the admission study, identified deceased controls from Leicestershire FHSA, and live controls from different general practices in Leicestershire. I visited all general practice surgeries, reviewed the case notes of surviving controls and completed the proformas.

The statistical analyses were done by Dr Nguyen-Van-Tam, Lecturer in Public Health and statistical advice was obtained from Dr Pearson, Senior Lecturer in Medical Statistics, both at Queen's Medical Centre, Nottingham.

However, I was involved in decision making and attended the analyses. I also conducted further statistical analyses for the chapters of influenza vaccine uptake and influenza vaccine effectiveness in reducing hospital admissions and risk factors for hospitalisation

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Publications arising from this work

Nicholson KG, Ahmed AH. Rapid Immune response to influenza vaccination. *Lancet* 1993;**342**:1494-5.

Ahmed AH, Nicholson KG, Influenza: treatment and prevention. *Postgraduate Doctor Middle East* 1995;**18**:384-90.

Ahmed AH, Nicholson KG, Nguyen-Van-Tam JS. Reduction in mortality associated with influenza vaccine during the 1989-90 epidemic. *Lancet* 1995;**346**:591-5.

Ahmed AH, Nicholson KG, Nguyen-Van-Tam JS. Is there a synergistic effect between previous and current vaccination against influenza?. *Lancet* 1995;**346**:1557P.

Ahmed AH, Nicholson KG. Efficacy of influenza vaccine. *Reviews in Medical Microbiology* 1996;**7**:23-30.

Ahmed AH, Nicholson KG. Influenza vaccination. *The Medical Book 1995/96*. Edited by M Hart. London:104-6.

Ahmed AH, Nicholson KG, Hammersley VS. The Contribution of Respiratory Viruses to Severe Exacerbations of Asthma in Adults. *Chest* 1996;**109**:588P.

Ahmed AH, Nicholson KG. Delays and diversity in the practice of local research ethics committees. *J Med Ethics* 1996;**22**:263-6.

Ahmed A H, Nicholson K G, Nguyen-Van-Tam J S, Pearson J C G. Effectiveness of influenza vaccine in reducing hospital admissions during the 1989 - 90 epidemic. Proceedings of 4th International Conference on the Prevention of Infection, Nice, France, May, 1996.

Nguyen-Van-Tam JS, Ahmed AH, Nicholson KG, Pearson JCG. Reduction in hospital admissions for pneumonia, influenza, bronchitis and emphysema associated with influenza vaccine during the 1989-90 epidemic in Leicestershire UK., in Brown LE, Hampson AW, Webster RG (eds): Options for the control of influenza. Elsevier BV, 1996, pp 107-112.

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Conference presentations

- Trent Regional Infectious Diseases meeting, Nottingham, UK, February, 1995. *Reduction in mortality associated with influenza vaccine during the 1989 - 1990 epidemic: a case-control study.*
- East Midlands Society of Physicians, Mansfield, UK, May, 1995. *Reduction in mortality associated with influenza vaccine during the 1989 - 1990 epidemic: a case-control study.*
- Options for Control of Influenza III Cairns, Queensland, Australia, May 1996. *Reduction in hospital admissions for pneumonia influenza bronchitis and emphysema associated with influenza vaccine during the 1989-90 epidemic in Leicestershire UK.*
- Fourth International Conference on the Prevention of Infection, Nice, France, May 1996. *Effectiveness of influenza vaccine in reducing hospital admissions during the 1989 - 90 epidemic.*
- British Thoracic Society Summer meeting, Loughborough, UK, July 1997. *Effectiveness of influenza vaccination in reducing mortality and hospital admissions for acute respiratory disease* (accepted for presentation).

Summary

Influenza epidemics impose an enormous burden in terms of morbidity, mortality, economic and social costs and are regularly associated with increased hospital admissions for acute respiratory disease. The 1989 - 90 influenza epidemic was the worst in the United Kingdom since 1976; it caused 29,000 deaths. Risk factors for influenza complications and deaths include chronic illness and residential care. In Britain annual influenza vaccination is strongly recommended for adults and children with chronic diseases (pulmonary disease including asthma, heart disease, renal failure, diabetes mellitus and other endocrine disorders) or immunosuppression caused by disease or treatment, and for people who live in residential care and other long stay facilities where rapid spread may follow the introduction of infection. Despite annual recommendations from the Department of Health less than 50% of high-risk patients are immunised each year. The reasons for the low immunisation rates are complex, but scepticism about vaccine effectiveness is partly responsible for the low uptake. The effectiveness of influenza vaccine in reducing certified influenza death (the mortality study) and hospitalisation for acute respiratory disease (hospital admission study) was assessed by two case-control studies.

Ethical approval for the study was obtained from 36 local research ethics committees covering the 38 District Health Authorities in England. The time to obtain ethical approval varied between 6 to 208 days; one third of the committees did not approve the project within 3 months, and three took longer than six months. There was considerable variation in the issues raised by local research ethics committees and none conformed exactly to Royal College of Physicians guidelines. Obtaining ethical approval for the multi-centre study was time consuming, and there was much diversity in the practice of local research ethics committees. The findings support the

recommendation for a central or regional review body for multi-centre studies.

General practitioners' records for 315 subjects whose primary or contributory cause of death was influenza between November 4, 1989, and February 23, 1990, and 777 controls, matched for age, sex, and area of residence, who died a year after the epidemic were reviewed. Information was collected on demography, usual place of residence (institutional or non institutional), and existence of chronic illness. Conditional logistic regression analysis for matched case-control studies showed that influenza vaccination reduced mortality by 41% (95% CI 13 - 60%) for all subjects. Among subjects who received the vaccine for the first time in 1989, vaccination reduced mortality by 9% (95% CI 0 - 50); however among those who had also been vaccinated previously, mortality was reduced by 75% (95% CI 31 - 91). There were no significant differences in the effect of vaccine between subjects who lived in institutions and in the community (p=0.16), or between subjects with high-risk medical conditions and those without (p=0.76). Influenza vaccine is effective in reducing mortality from influenza, and effectiveness seems to be greater after repeated annual vaccination that after first time administration.

Vaccine up-take among cases and controls was only 21.5% but 77% of individuals had an indication for vaccination as recommended by the DoH. There was no significant difference in the proportion of patients in each of the DoH high-risk groups who were vaccinated (x^2 =7, p = 0.07). Multiple logistic regression showed that three factors significantly affected the likelihood of immunisation in 1989 - 90: more frequent consultations with GP during the 12 months before death (OR 1.04, CI 1.03 - 1.04), living in residential care (OR, 1.45, CI 1.17 - 1.79), and 'previous' vaccination (between 1985 - 88) (OR 7.61, CI 6.06 - 9.56).

Of the 315 fatal influenza cases identified 299 (94.9%) were 65 years or older and 263 (83.5%) had an indication for vaccination. Details on duration

of final illness were available for 275. Of these 46 (17%) died within the first 48 hours after onset of final illness and (64%) died within the first seven days. Because of the rapid deterioration following onset of illness emphasis should be put on prevention as the most effective mean of reducing mortality.

All patients 16 years or older who were admitted to 15 Leicestershire hospitals for pneumonia, influenza, bronchitis, or emphysema between December 1, 1989, and January 31, 1990 were identified with the goal of assessing vaccine effectiveness in preventing hospital admissions. A total of 303 patients were admitted representing a 42% increase when compared with the mean number of admissions during the corresponding periods in 1987/88 (n=172), 1988/89 (n=261), and 1990/91 (n=205). In-patient records were successfully retrieved for 264 admissions. Primary care records were accessed (to collect information on vaccination) for 156 of these admissions. Hospital and general practitioners' records for the 156 admissions and 289 controls matched for age and sex were reviewed for information on demography, the usual place of residence (institutional or non-institutional), and the existence of chronic illness. Conditional logistic regression analysis for matched case-control studies showed that influenza vaccination reduced hospital admissions by 63% (955 CI 17 - 84%). There was no significant difference in vaccine effectiveness between subjects who were previously vaccinated and those who received vaccine for the first time in 1989 ($p = 0.82$). Similarly, there was no significant difference in vaccine effectiveness between subjects with 'high-risk' medical conditions and those without ($p = 0.23$), nor between subjects living in residential care and those living in their own homes ($p = 0.88$). However, there was a strong trend towards improved vaccine effectiveness when used in institutional settings.

Details of hospitalisation of the 264 admissions with acute respiratory illness showed their median (range) age was 77 (16 - 99) years. More than three quarters of these admissions were aged 65 years or over. Antibiotics

were prescribed during hospitalisation for more than 80%, respiratory medications for 31%, and cardiovascular medications for 14%. The median (range) duration of hospitalisation was 7 (1 - 54) days. More than one third stayed in hospital for more than ten days and over one in ten were inpatients for three weeks or more. A total of 216 (81.8%) patients had at least one full blood count, 211 (79.9%) had at least one biochemistry test, and 207 (78.4%) had at least one radiological investigation. Based on a randomly selected sample of 50 admissions the average cost of medications and investigations per admission was estimated at £102.36.

INTRODUCTION

CHAPTER 1

Historical background

1.1 Introduction

Influenza is an acute, usually self limited, febrile respiratory illness caused by influenza type A or B virus. Influenza C virus rarely, if ever, produces the influenza syndrome (Mogabgab, 1963). The illness is characterised by abrupt onset of systemic symptoms including headaches, backache, myalgia, shivering and malaise, accompanied by respiratory symptoms, particularly dry cough, stuffy nose, and sore throat. The acute symptoms persist for about four days and then gradually improve in uncomplicated cases. The illness may, however, be complicated by hyperpyrexia, acute tracheobronchitis, primary influenza viral pneumonia, secondary bacterial pneumonia, myositis and myoglobinuria, transverse myelitis, encephalitis, toxic shock syndrome, otitis media, and Reye's syndrome in children.

Influenza in man occurs in two epidemiologic forms: pandemic influenza which results from the emergence of a new influenza A virus to which the population possesses little or no immunity, so it spreads with a high attack rate in all parts of the world; and interpandemic influenza A or B, occurring as sporadic infections, a localised outbreak, or epidemic. Epidemics represent an outbreak in a given community and are associated with significant drift of the surface haemagglutinin and neuraminidase antigens. Epidemics of variable extent and severity occur almost every winter and result in significant morbidity in the general population and increased mortality in 'high-risk' individuals; they impose an enormous burden in terms of economic and social costs.

1.2 History

The origin of the term 'influenza' is uncertain. It was apparently given by its victims in the middle of the 18th century (Creighton, 1891). It is unclear whether the term influenza referred to 'influenza di fretto' [influence of the cold] (Francis, 1959), or used in reference to the possible 'influence' of the planets at times of respiratory epidemics (Stuart-Harris and Schild, 1976). 'Influenza' was used in England during the outbreak of 1743 (Francis, 1953), but earlier references to the illness included 'newe acquayantance', the gentle correction, epidemic catarrh, or catarrhal fever (Francis, 1953; Creighton, 1965).

Influenza is defined as much by its epidemiology as by its clinical picture, and its causative virus rapidly and progressively changes. Historical considerations are therefore important in defining and evaluating this illness. Although influenza lacks the pathognomonic features of diseases such as smallpox, measles, or poliomyelitis to permit its unequivocal recognition by the casual observer, a combination of the explosive nature of the illness, its tendency for seasonability, high attack rate, and respiratory and systemic features allow an overview of the disease since ancient times.

Langmuir *et al.*, 1985 proposed that the 'plague of Athens' in the years 430 - 427 B.C. was caused by influenza associated with toxic shock syndrome. He named the association the Thucydides syndrome after an Athenian general who acquired the illness but lived to record its outbreak in *The story of the Peloponnesian War.* However, proposals as diverse as smallpox and exanthematic typhus have been suggested as possible causes of the 'plague', and the exact nature of this epidemic will remain a mystery (Theodorides, 1995).

The epidemic in 412 B.C. described by Hippocrates was probably influenza (Pryor, 1964). He described in detail a respiratory disease that: "broke out about Solstice (December 22) and was preceded by marked

changes in the winds. There was a great tendency to relapses and it was further complicated by pulmonary affection." He thought that women were not as likely to be affected as men "because they do not expose themselves to the air as do men." Clearer historical accounts of influenza epidemics every two to three years can be traced back to the twelfth century (Hirsch, 1883). Thompson, 1852 described 22 outbreaks occurring between 1510 and 1890. Sydenham's account of an outbreak that occurred in 1679 provides a clear description of influenza: "... In the following year, viz. 1679, these intermittents reappeared at the beginning of July and increasing every day proved very violent and destructive in August. But having already treated of these at large, I shall only observe, that they gave way to a new epidemic which proceeded from the manifest qualities of the air in November. For the beginning of this month a cough arose, which was more epidemic than I had hitherto observed; for it seized nearly whole families at once. Some required little medicine, but in others the cough occasioned such violent motion of the lungs, that sometimes a vomiting and vertigo ensued. On the first days of the disorder, the cough was almost dry and expectoration not considerable, but afterwards the matter in some measure increased. In short, from the smallness of expectoration, the violence of the cough and the duration of the coughing fits; it seemed greatly to resemble the convulsive hooping cough of children, only it was not so severe. But was attended with a fever and its usual concomitants, in which particular it exceeded the convulsion cough, for I never knew that accompanied with those symptoms ....." (Sydenham, 1955).

Pandemics, however, occur less often. Probably the first pandemic that fits the description of influenza occurred in 1510 (Hirsch, 1883). Since then 11 pandemics have been described (Kilbourne, 1987). The 1847 - 48 pandemic was associated with a 20-fold rise in deaths in London as compared with the average for same period during the seven preceding years (Parsons , 1891).

Another influenza pandemic occurred in 1889 - 90. The first cases were

described in Central Asia and then spread west across Russia to Western Europe. The number of 'influenza' deaths in London increased by 55-fold during the first quarter of 1890 as compared with the 5 preceding winters (Parsons, 1891).

The greatest pandemic occurred in 1918 - 19 and was responsible for 21 million deaths world-wide and 675,000 in the United States alone (Crosby, 1976). During this pandemic, the mortality rate in England and Wales increased more than tenfold to 3129 per million (Stuart-Harris *et al.*, 1985). Unlike other epidemics during the nineteenth and twentieth centuries high mortality was seen in otherwise healthy young adults. During the 1918 - 19 pandemic only 19% of the deaths was among those 55 years or older, whereas during the 1957 and 1968 pandemics the percentage among those 55 years or older was 73 and 84% respectively (Stuart-Harris *et al.*, 1985). The striking feature of this epidemic was the large number of cases with pneumonia particularly among adults aged 20 to 40. In this age group the case-fatality rate was about 50% (Ministry of Health, 1920). However, this may not be unique in the history of influenza as similar observations were noted during the 1782 pandemic (Francis, 1953).

The modern era of the understanding of influenza began in 1933 with the isolation of influenza A virus in ferrets (Smith *et al.*, 1933). Influenza B virus was subsequently isolated in 1939 (Francis, 1940), and influenza C in 1950 (Taylor, 1951). In 1936 the virus was grown in embryonated hens' eggs which allowed extensive studies of the properties of the virus leading to the development of inactivated vaccine (Burnet, 1936). The phenomenon of haemagglutination was discovered in 1941 (Hirst, 1941). This has led to a simple and inexpensive method of measuring virus antibody.

Identification of specific antibodies in the sera of elderly people has allowed more precise description of previous outbreaks and their sequential appearance (serological archaeology). Such retrospective investigations are

obviously limited by the life-span of man and the date on which the blood samples were taken. Within these constrains, our backward reach has extended to the middle of the nineteenth century. Ninety percent of subjects born between 1857 and 1877 were found to have antibodies to Hong Kong (H3) virus prior to its epidemic reappearance in 1968; 26% had pre-epidemic antibody to virus of the H2 'Asian' subtype that caused the pandemic of 1957 (Masurel and Marine, 1973). This and other studies (Davenport, 1977) provide evidence for the sequential appearance of H2 and H3 viruses in the last decade or so of the last century. Rekart *et al.*, (1982); Masurel and Heijtink, (1983) presented serological evidence for the circulation of H1N1 viruses between 1908 and 1918. This taken together with evidence for H3 prevalence at the same time and earlier implies that the co-circulation of H1 and H3 subtypes since 1977 is not without precedent. Serological archaeology indicates with little doubt that the cause of the great 1918 pandemic is a virus antigenically similar to the swine influenza virus (H1) (Shope, 1958).

Epidemics since 1933 were identified by virus isolation. The first undisputed pandemic in the virologic era occurred in 1957 and was caused by an A/Asian/57(H2N2) virus. The pandemic started in China at the beginning of 1957 and then spread east and west (Stuart-Harris and Schild, 1976). In Britain deaths from influenza in the 1957 pandemic reached a peak in October and the total death toll was estimated at 33,000 (Ministry of Health, 1960).

Another pandemic, again arising in the far east, followed in 1968. Hong Kong influenza (H3N2) virus attacked a partially immune population due to the related N2 neuraminidase of the antecedent H2N2 virus, and has persisted to this day. The pandemic started in Hong Kong during mid-July 1968 and then spread east and west. In Britain there was little general spread until the autumn and the disease was generally mild. In contrast to the Asian

pandemic in 1957 the age-specific attack rates of all age groups were similar (Davis *et al.*, 1968; Hope-Simpson, 1970).

In 1977 a new antigenic variant appeared, A/USSR/77 (H1N1). The origin of this virus was however, subsequently traced to mainland China. Although this virus had changes of both the haemagglutin and neuraminidase it did not cause a pandemic. This may have been because most of the world's population in 1977 were alive before 1957 during the previous H1N1 era. The new virus was confined almost entirely to people under the age of 23 years. Once again, this new variant did not displace the virus of H3N2 subtype that had persisted since 1968. H1N1 and H3N2 viruses both continue to circulate throughout the world since 1977.

CHAPTER 2

Influenza viruses

2.1 Introduction

Influenza viruses belong to the family Orthomyxoviridae which contains two genera: influenza virus type A and influenza virus type B. Influenza virus type C probably represents another genus, although it has not yet been so classified (Fenner, 1976). The nomenclature of a particular influenza virus is based on the virus type, geographic origin, strain number, and year of isolation. For influenza A viruses, the type designation is followed in parentheses by the subtype classification. With the advent of cell culture in the 1950s, additional methods for preparing virus stocks have become available. In the last decade there has been an enormous explosion of information on virus structure and genetics. This has been achieved employing new techniques such as modern protein chemistry particularly X-ray crystallography, gene sequencing through cDNA methods, and use of monoclonal antibodies for selection of virus with point mutations in their haemagglutinins leading to resistance to neutralisation.

The morphologic characteristic of all influenza virus types, subtypes and strains are similar. Electron microscopy studies show them to be enveloped viruses covered with surface projections. Their size is estimated to be 80 - 120 nm in diameter. Particles of standard laboratory strains are mainly spherical; newly isolated strains contain many elongated filamentous forms which vary in length and may reach to 40 nm. Eight proteins have been identified in influenza viruses: three polymerase proteins (PB1, PB2, and PA); haemagglutinin (HA); neuraminidase (NA); nucleoprotein (NP); matrix (M); and two non structural proteins (NS1 and NS2) (Chopin and Compans, 1975). The surface spikes are glycoproteins that possess either haemagglutinin or neuraminidase activity. The envelope is composed of a lipid bilayer. Within

the envelope are eight segments of linear, rodlike structures of nucleoprotein (NP), with which the polymerase proteins PB1, PB2 and PA are in close association in an RNP complex (Heggeness *et al.*, 1982).

Influenza C viruses share most of the biochemical properties of influenza A and B viruses. However, they have only seven RNA segments, do not possess a neuraminidase, and have a single external glycoprotein spike resembling the haemagglutinin of influenza A and B (Heggeness *et al.*, 1982).

2.2 The envelope

The envelope is composed of a host cell derived lipid bilayer on the inner surface of which is a layer of protein called matrix (M1) protein (Kendal *et al.*, 1977). The lipid bilayer serves to provide stability to the virus particles (Karadaghi *et al.*, 1984). The hydrophobic ends of the HA and NA peplomers are attached to the outer layer of the lipid bilayer but do not penetrate within it.

Recent evidence indicate that the M1 protein is essential for late phase of virus replication and its absence interferes with budding (Rey and Nayak, 1992). Another important component of the virus envelope is the M2 protein. It is the product of a spliced mRNA of the M gene (Hugley, 1992). The M2 protein seems to modulate the pH within the pathway through which virus is transported. It functions in the later stages of virus replication and causes an increase in pH allowing transport of pH sensitive HA to the cell surface (Skehel and Wiley, 1995). M2 protein also serves as a type specific antigen.

2.3 Nucleocapsid (Ribonucleoprotein)

The nuclecapsid of influenza virus exists in the form of discrete segments, each of which contains one molecule of viral RNA, multiple copies of the NP polypeptides, and probably one or more polymerase (P) proteins, two basic

(PBI and PB2) and one acidic (PA) subunits (Ishiama *et al.*, 1993). The NP protein is the subunit of the helical nucleocapsid and possesses the type-specific antiginicity on which the classification of influenza into A, B, and C types is based (Pons *et al.*, 1969).

2.4 Haemagglutinin

The haemagglutinin (HA) molecule is a trimer of identical subunits, each of which contains two polypeptide chains, HA_1 (molecular weight 50,000) and HA_2 (molecular weight 27,000). HA_1 and HA_2 are formed by proteolytic cleavage of the primary translation product HA_0 of mRNA for HA. The HA is one of the major antigens of influenza virus compromising 30% of the protein of the virion, and is the protein most frequently involved with antigenic variation. There are large differences in amino acid sequences in HA among different subtypes of influenza A, whereas in closely related strains only small differences are observed (Webster, 1972). The degree of amino acid differences may be directly related to degree of antigenic variation.

2.5 Neuraminidase

Neuraminidase (NA), like HA, is one of the important antigens of influenza virus. NA constitutes about 5% of the protein of the virion and each has a molecular weight of 240,000. It contains antigens common to each subtype and also shows some antigenic variation within a subtype. NA secretes an enzyme that catalyses cleavage of the α-ketosidic linkage between terminal sialic acid and adjacent sugar residue and plays a role in the pathogenesis of infection (von Itzstein *et al.*, 1993).

2.6 Transmission and virus shedding

Influenza virus infection is acquired by the transfer of virus-laden respiratory secretion from an infected to a susceptible person. Small particle aerosols seem to be the predominant factor in such person-to-person transmission (Douglas, 1975). Influenza A virus has been shown to be relatively stable in small particle aerosols at a variety of relative humidities ranging from 15 - 40% (Hemmes *et al.* 1960). In temperate climates influenza generally is a winter disease occurring during the period when the relative humidity indoors is low as result of heating, and when survival of virus in air is optimal (Hemmes *et al.* 1960). Furthermore in experimental infections, doses of 137 - 300 times the median tissue culture infective dose ($TCID_{50}$) are required to infect by nasal drops, whereas 0.6 - 3.0 ($TCID_{50}$) is infectious by the aerosol route (Alford *et al.* 1960, Little *et al.* 1979).

Quantification of virus in respiratory tract specimens reveals that virus is first detected just before the onset of illness (within 24 hours), rapidly rises to a peak, remains elevated for 24 - 48 hours, and then rapidly decreases to low titres. Usually influenza virus is no longer detectable in adults after 5 - 10 days (Douglas, 1975). Although the severity of illness correlates temporally with quantities of virus shed in experimental influenza, it is not known whether such a correlation holds for natural influenza (Douglas, 1975).

2.7 Pathogenesis

Proteolytic cleavage of the influenza virus haemagglutinin glycoprotein into HA_1 and HA_2 by an intracellular protease at multiple basic amino acids is prerequisite for formation of infectious influenza (Rott *et al.*, 1995). Following this the HA fuses with cell membrane, after which the virion is taken into the cell by endocytosis and these two steps are physiologic requirements for infection to take place (Rott *et al.*, 1995). The neuraminidase (sialidase) also plays a role in the pathogenesis of influenza. It is involved in the elution of

newly synthesised virions from infected cells, and may also assist in movement of virus through the mucus within the respiratory tract (von Itzstein *et al.*, 1993).

Viral glycoproteins are activated, in general, by serine endoproteases secreted from epithelial cells. Host protease present in the inflammatory response were found to activate some strains of influenza (Rott *et al.*, 1995). In addition secreted bacterial enzymes have been found to be involved in activation of the HA glycoprotein. *Staphylococcus aureus* and *Aerococcus viridans* secrete a trypsin-like protease which activated influenza virus under *in-vitro* conditions and in a mouse model of infection (Scheiblauer *et al.*, 1992). After co-infection of mice with virus and bacteria or after application of the isolated bacterial enzymes simultaneously with the virus, high virus titres were detected in the lung, resulting in a fatal disease with extended lung lesions. Interestingly, enzymes from different *Staphylococcus aureus* strains were only able to activate the haemagglutinin of certain influenza virus strains. Thus the right virus has to encounter the right bacterium to develop the synergistic pathogenic effect. In further experiments, staphylokinase and streptokinase were found to activate the proenzyme plasminogen to plasmin, which can also cleave haemagglutinin (Scheiblauer *et al.*, 1992). Pathogenic influenza, therefore, seems to result from a complex interplay of factors that are determined by the characteristics of the virus, bacterial co-infection and the inflammatory response of the infected host.

The major pathophysiologic effects of influenza on the respiratory tract are increased airway reactivity and impaired mucociliary clearance. Influenza induces airway hyperreactivity both in normal subjects and patients with asthma (Little *et al.*, 1978; Beasley *et al.*, 1988). Proposed mechanisms for the bronchospasm are the release of mediators by inflammatory cells in the region of infection and vagal as well as other neural reflexes stimulated by epithelial damage from the infection (Leigh, 1991). Factors contributing to

impaired mucociliary clearance include necrosis and desquamation of ciliated cells, clumping of cilia as a result of virus attachment to more than one cilium, acquired ciliary microtubular defects and altered mucus secretion (Leigh, 1991).

CHAPTER 3
Epidemiology

3.1 Influenza surveillance

Influenza virus has been internationally monitored for many years by the World Health Organisation (WHO). The main objective of WHO influenza reference laboratories is to identify the different virus subgroups in circulation in order to identify strains for vaccine production. The influenza epidemics themselves are monitored using health service based indicators (Quenel *et al.*, 1994; Fleming *et al.*, 1995). These include: home visits and consultations per week irrespective of diagnosis, consultations per week for influenza-like illness activity; absenteeism from work; drug consumption; hospital activity including short term admissions to medical wards, and number of deaths.

In the UK. the largest clinical surveillance network is the Royal College of General Practitioners' weekly returns service. However, virological surveillance is based mostly on the results of virological tests of patients admitted to hospital with centralised reporting to the Public Health Laboratory Service. Recently a system combining clinical and virological surveillance in primary care has shown improved influenza monitoring and detected peak influenza virus activity five weeks before those reported by the Public Health Laboratory Service (Fleming *et al.*, 1995).

Quenel *et al.*, (1994) used an influenza A surveillance system to estimate the sensitivity and specificity of different kinds of health service based indicators compared with a virological indicator. An epidemic week was defined as week during which $\geq 1\%$ of the specimens collected were positive for influenza virus A (virological 'gold standard'). Using this definition they found that overall the health service based indicators began to increase before virological indicators. The emergency visit indicator was the

earliest indicator (1 - 4 weeks before the virologic indicator), followed by sick-leave reports (1 - 3 weeks). Increases in GP overall activity was noted 1 - 2 weeks before virological indicator. Influenza-like illness diagnosed by GPs were reported 0 - 1 week beforehand. When comparing epidemic weeks identified by the 'gold standard' and those identified by statistical thresholds, two types of health service based indicators were distinguished: those which were more specific than sensitive (overall activity of GPs due to influenza like illness, drug consumption, and hospital fatality) and those which were more sensitive than specific (emergency home visits, and absenteeism from work). Overall the specificity of the health services based indicators was around 70%.

3.2 Antigenic variation

Influenza viruses have a unique and important feature of changing antigenicity. Antigenic variation is a frequent, almost annual, phenomenon with influenza A virus, but occurs less frequently with influenza B virus. Influenza continues to be a major human epidemic disease due to antigenic variation which involves the HA and NA principally (Air *et al.*, 1990). However, the virion structural and non structural proteins may also vary (Wiley *et al.* 1987). Antigenic variation is referred to as antigenic shift or antigenic drift depending on whether the variation is great or small. Antigenic drift is the consequence of relatively minor changes that occur frequently within an influenza virus subtype. It is generally accepted to result from mutation(s) affecting the RNA segment coding for either the HA or less commonly NA (Webster *et al.*, 1980). Antigenic shift occurs with the introduction of a new haemagglutinin and/or neuraminidase and usually heralds pandemic influenza.

The mechanism of antigenic shift with the introduction of a new segment of RNA resulting in a new surface glycoprotein can be explained by genetic reassortment. Maps of tryptic peptide digests of HA subunits reveal

marked changes of amino acid sequence among haemagglutinins obtained from H2- and H3-containing viruses (Laver and Webster, 1968). Studies of polyacrylamide gel electrophoresis of the genomes of viruses of different subtypes reveal that RNA segments coding for the HA and NA from different types migrate to different positions on the gel, which indicates that segments of RNA coding for either the HA, NA, or both are markedly different for different subtypes (Scholtissek *et al.*, 1977).

It is well recognised that genetic reassortment among influenza viruses takes place frequently in eggs and in tissue culture (Kilbourne *et al.*, 1971). Recently there has been much speculation concerning the species in which 'new' human reassortants might arise and avian and porcine species seem important. The pandemics of 1957, 1968, and 1977 all began in mainland China and then spread east and west (Kilbourne, 1975). It is reasoned that China is the source of pandemic strains because swine, birds and humans live under the same roof, thereby providing the opportunity for the admixing of avian and human viruses in pigs (Scholtissek *et al.*, 1978).

3.3 Epidemic influenza

Influenza epidemics begin abruptly, reach a peak in 2 - 3 weeks, and last for 5 - 6 weeks (Glezen *et al.*, 1976). The highest attack rate is among the young, and reports of school children with respiratory virus illness are often the first indication of epidemics (Glezen *et al.*, 1976). Outbreaks in children are soon followed by influenza-like illness among adults, then increased hospital admissions for patients with pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD) and congestive heart failure. Increased numbers of deaths due to pneumonia and influenza lag behind other indicators due to the interval from the onset of illness to time of death and the delay in registering deaths and reporting the figures to public health officials (Glezen *et al.*, 1982).

An interesting hypothesis is that influenza outbreaks may generate from asymptomatic carriers who reactivate virus from a latent state and then transmit to susceptible individuals (Hope-Simpson, 1992). The hypothesis proposes that the virus remains non-infectious in some mode of persistence or latency in persons recovered from influenza and would only become infectious when a seasonally mediated stimulus reactivated the virus in their tissues. This hypothesis is supported by observations that outbreaks occurred simultaneously in geographic locations far removed from one another without any possibility for direct contact, and often an outbreak starts in a school for children or a nursing home. The explanation suggesting that the epidemic consists entirely of individuals who have caught the virus from carriers (infected in a previous epidemic) in whom persistent non infectious virus has been briefly reactivated also explains the puzzling phenomenon of epidemics ceasing before all susceptible individuals are affected.

Pandemic influenza results from the emergence of a new virus to which the overall population possesses little or no immunity so that epidemics of influenza progress to involve all parts of the world. The most severe pandemics have resulted when both surface antigens are replaced (Kilbourne, 1975). However, there are exceptions to this generalisation: A/USSR/7/H1N1 did not cause a severe pandemic in spite of major shifts in both surface glycoproteins. It appears that the transmissibility from person to person and intrinsic virulence (severity of the disease) are virus-determined functions that may vary as much as antigenicity. For example, the intrinsic virulence of H1N1 viruses since 1978 appears to be less than of H3N2 (Monto *et al.*, 1985).

3.4 Infection rates

Influenza epidemics are associated with significant morbidity in the general population. Investigations of respiratory virus illnesses and infection in

Tecumseh, Michigan carried out over 11 years encompassed influenza A (H3N2) outbreaks during two seasons: 1977 - 8 and 1981 - 2 (Monto and Sullivan, 1993). The highest, serologically determined, infection rates of 23 to 42% were among children less than 10 years of age. For those 20 years of age and over the infection rate remained in the 10 to 20% range. Influenza A (H1N1) caused outbreaks in 1977 - 8, 1978 - 9, and 1980 - 1. The A (H1N1) viruses reappeared in 1977 - 8 after a global absence of approximately 20 years. Infection rates were 50% in the 15 - 19 year olds, 29% in the 10 to 14 year olds, and 11% in the 5 to 9 years olds. In this year major outbreaks were experienced on many university campuses but with less activity in the community. However, in 1978 - 9 community outbreaks were recognised, involving considerable school absenteeism and infection rates were over 50% in the 5 to 14 year olds and approximately 28% in the under five and 15 to 19 age groups. In the third influenza A (H1N1) outbreak in 1980 - 1, the infection rates were considerably lower than in either previous outbreaks: about 16% in the 5 to 14 year olds, and 13.5% in the 15 to 19 year olds. However, in the under five year olds the infection rates were 10.8%. Remarkably small numbers of infections were detected in individuals who lived through the previous A (H1N1) period that terminated in 1957. Infection frequencies for influenza B were similar in overall age-specific pattern to those seen with influenza A (H1N1).

Overall there was a clear increase in frequency of illness in women aged 20 to 34 years when compared with men of the same age. Furthermore, non-employed women had consistently higher respiratory illness rates when compared with employed women of the same age. This can be explained by greater exposure of women to children. Pre-school and school-age children undoubtedly play a major role in the spread of influenza viruses. Taber *et al.*, (1981) noted that the incidence of infection and illness attributed to influenza

among persons with school children was more than double that in families without children attending school or day care facilities (38.5% *vs.* 16.9%).

CHAPTER 4
Human influenza

4.1 Clinical features

Infection with influenza viruses can result in a wide spectrum of clinical responses ranging from asymptomatic infection to fulminant primary viral pneumonia. The variation in both the severity of illness and proportion of subjects with complications in different groups result from age difference, pervious health, and immunological status.

Influenza A and B viruses cause the same spectrum of disease. The frequency of severe influenza B infections requiring hospital admission may be several-fold less than that for influenza A. In a recent survey in the Netherlands, among 213 influenza isolates, 85 from hospitalised patients and 128 from the general practice setting, only two were H1N1 whereas 89 were H3N2 and the remainder were influenza B. The ratio between influenza A (H3N2) versus influenza B virus isolates was significantly higher among hospitalised patients as compared with those from general practitioners (55/29 versus 34/93; $p < 0.001$) (Claas *et al.*, 1995). Other reports have, however, shown them to be similar (Perrotta *et al.*, 1985). In contrast, influenza C infection, when it occurs, causes afebrile common colds and rarely, if ever, produces the influenza syndrome (Mogabgab, 1963).

4.2 Uncomplicated influenza

The onset of the illness is typically abrupt after an incubation period of 1 - 2 days. Initially, systemic symptoms predominate and include: feverishness, chills, rigors, headaches, myalgia, malaise, and anorexia; arthralgias may also be observed. Headache and sore throat are the most frequent symptoms. The early features are almost invariably accompanied by a non-productive cough, sneezing, nasal discharge or obstruction. Ocular symptoms including

lacrimation, burning and pain in the eye muscles elicited by eye movements may also occur in some cases.

Fever is the most important physical finding. The temperature usually rises to 38^0C - 40^0C and occasionally to 41^0C. The pyrexia peaks at the height of systemic features and is typically of three days duration but may last up to eight days. The patient appears toxic, the skin is often hot and moist, the face appears flushed, the eyes watery and reddened. The mucus membrane of the nose and throat are hyperaemic but devoid of an exudate. Small, tender cervical lymph nodes are palpated in up to a quarter of all cases and crackles and wheeze are heard in a similar proportion. These symptoms and signs typically persist for 3 to 4 days, but cough, lassitude, and malaise may persist for up to two weeks (Douglas, 1975).

Manifestations of uncomplicated influenza in children are usually similar to those in adults. However, influenza in neonates is thought to be mild. Puck *et al.*, (1980) found that in 26 infants under four months of age from whom influenza A virus was recovered, 50% (13/26) suffered febrile upper respiratory illness or fever alone and 27% (7/26) had afebrile upper respiratory illness; the remaining six (23%) had croup, bronchitis or pneumonia. In these infants the protection afforded appears to result from transplacental antibody. However, in infants older than four months no such protection was discernible indicating that this passive immunity may be short.

4.3 Influenza complications

Pulmonary complications

Two types of pneumonia associated with influenza are well recognised: primary influenza viral pneumonia and secondary bacterial infection. In addition other pulmonary syndromes often occur during influenza epidemics

including laryngotracheo-bronchitis and exacerbations of asthma and chronic obstructive pulmonary disease.

The syndrome of primary influenza viral pneumonia was first well documented in the 1957 - 1958 epidemic. Martin *et al.*, (1959) reported 12 patients among 29 fatal pneumonia cases complicating influenza. However, it is clear that some of the deaths in 1918 - 1919 epidemic were due to this syndrome. A letter from a physician working in Boston during the 1918 -1919 epidemic describes the syndrome: " ... These men start with what appears to be an ordinary attack of LaGrippe or influenza, and when brought to the Hosp. they very rapidly develop the most viscious type of pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours latter you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of few hours until deaths comes, and it is simply the struggle for air until they suffocate. ... There is no doubt in my mind that there is a new mixed infection here, but I don't know. My total time is taken up hunting Rales, rales dry or moist, sibilant or crepitant or any other of the hundred things that one may find in the chest, they all mean one thing here -Pneumonia- and that means in about all cases death" (Grist, 1979).

After a typical onset of influenza, there is rapid progression of fever, cough, dyspnoea, and cyanosis. Physical examination and chest X-ray of hospitalised cases reveal bilateral findings but no consolidation (Winterbawer *et al.*, 1977). Blood gas studies show marked hypoxia, Gram stain of the sputum reveals no significant bacteria, and bacterial culture yields sparse growth of normal flora. Viral cultures yield high titres of influenza A virus. Treatment is aimed at aggressive respiratory and haemodynamic support but the mortality rate may still be high. Winterbawer *et al.*, (1977) reported 11 patients with primary viral pneumonia. Of the 11 patients only 5 survived

after prolonged ventilation and oxygen therapy. Of the 6 patients who died 4 enjoyed good health prior to their terminal illness but 2 had previously diagnosed lymphoproliferative malignancies.

The pathological features of primary influenza pneumonia are non-specific. Fatal cases show signs of necrotising tracheobronchitis which may progress to organised diffuse alveolar damage with variable degree of fibrosis. Non-fatal cases show mild alveolar damage manifesting as fibrinous exudates and alveolar septal oedema which may progress to patchy organisation including bronchiolitis obliterans with organising pneumonia (BOOP) (Yeldani and Colby, 1994). Interestingly the two cases with BOOP in the series reported by Yeldani and Colby, (1994), responded to steroids with complete resolution of their lesions indicating that steroids may play a role in the treatment of primary influenza viral pneumonia.

Secondary bacterial pneumonia

Secondary bacterial pneumonia often produces a syndrome that is clinically indistinguishable from that occurring in the absence of influenza. The patients usually have classic influenza illness followed by a period of improvement lasting a few days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and pulmonary consolidation detected on physical examination and chest x-ray. In a series of 20 patients reported by Martin *et al.*, 1959, 11 (55%) died. Among those who died, 6 (54%) had underlying chronic disease whereas this was documented in 3 (33%) of those who survived. Gram staining and culture of sputum reveal a predominance of a bacterial pathogen, most often *Streptococcus pneumoniae, Staphylococcus aureus,* or *Haemophilus influenzae* (Schwarzmann *et al.*, 1971). However, during influenza outbreaks many cases are observed that do not fit into either of the

aforementioned categories. These patients may have mixed viral and bacterial infection.

Croup

A significant number of cases of laryngotracheo-bronchitis (croup) occur during influenza outbreaks. Spelman and McHardy, (1985) studied clinical features of 151 admissions with influenza during concurrent outbreaks of influenza A and B in 1982 in Australia. Croup occurred in 44% (10/23) of children five years or less. The incidence dropped steadily with increasing age and in those aged 60 years or over only one patient of 33 had croup. Of the ten children with croup one required tracheostomy. There was no difference in incidence of croup between those who had influenza A or B infection.

Bronchitis and asthma

Acute bronchitis is the most common lower respiratory tract complication of influenza. Connolly *et al.*, (1993) found evidence of acute bronchitis in about one fifth of all subjects infected with influenza during the H3N2 epidemic in 1989 - 90.

In normal individuals with uncomplicated influenza pulmonary function tests have revealed airway hyperreactivity, peripheral airway dysfunction, and abnormalities in gas exchange that may persist for weeks after clinical recovery (Horner and Gray, 1973; Little *et al.*, 1978). Studies in children with asthma or wheezy bronchitis have shown that about 80% of laboratory confirmed viral infections, including influenza, are associated with asthma exacerbation (Johnston *et al.*, 1995). Kondo and Abe, (1991) studied 20 asthmatic children aged eight to 12 years following serologically confirmed influenza. FEV1 began to decrease with onset of illness in 15 of the 20 patients. Maximum mean decrease, of 30% from baseline, was noted during

the second day. Although improvement was observed on the third day, the drop in FEV1 lasted for more than 10 days. Similarly, about 60% of viral infections in adult patients with asthma are associated with exacerbations (Beasley *et al.*, 1988).

Myocarditis

Myocarditis seems to be an occasional complication of influenza. In a prospective study in a military hospital during an influenza A outbreak, six of 41 serologically confirmed cases of influenza had acute myocarditis on the basis of serial electrocardiographic ST segment and/or T wave changes (Karjalainen *et al.*, 1980). Echocardiography revealed regional myocardial dysfunction in all patients with influenza myocarditis, and MB-CK isoenzyme was elevated in three of the six patients (Karjalainen *et al.*, 1980).

Oseasohn *et al.*, (1959) found evidence of acute myocardial involvement in 13 of 33 fatal influenza cases. In three the lesion was confined to the myocardial arterioles, and in 10, 8 of whom were less than 40 years, the process involved the interstitium and the muscle fibres in varying degree. Virus was obtained from the myocardium in one case.

Neurological complications

A range of neurological complications have been described in association with influenza infection including: irritability, confusion, convulsions psychosis, neuritis, Guillain-Barré syndrome, transverse myelitis, and encephalomyelitis. Wells, (1971) described 19 patients with neurological disorders following upper respiratory tract infection during the winter of 1969-70 when influenza A was epidemic. All patients gave a history of influenza-like illness, but only eight had serological evidence of influenza. Spinal and radicular syndromes predominated; 13 patients had a predominantly spinal disorder, eight of whom had myelopathy, four had a

combination of signs indicating both spinal and radicular disease, and one with encephalopathy was found to have a diffuse myelopathy when she emerged from coma.

Protheroe and Mellor, (1991) described two children with influenza A encephalitis during the A/England/427/88 (H3N2) 1989-90 epidemic. In both children the encephalitis developed within three days of respiratory symptoms and both became comatosed within 48 hours. Virological studies showed that the patients had had influenza A infection. Computed tomography demonstrated symmetrical localised hypodense lesions within the thalami and pons. Interestingly, similar radiological findings were reported from Japan (Hattori *et al.*, 1983), suggesting that there may be a typical appearance on computed tomography in influenza encephalitis.

Myositis, myoglobinuria and renal failure

Unlike myalgia that occurs early during the course of influenzal illness, Myositis and myoglobinuria usually occur in the recovery phase. Myositis and myoglobinuria have been reported mostly in children after influenza A or B infection. The five largest series of cases of acute childhood myositis that have been reported include 162 patients. Results of viral studies were reported in 77 cases; 48 (62%) of the 77 cases were infected with influenza B virus and 19 (25%) were infected with influenza A virus (McIntyre and Doherty, 1995). The typical clinical features include severe calf pain and tenderness, abnormal gait or refusal to walk, preservation of muscle power, and pain on dorsiflection (McIntyre and Doherty, 1995).

The condition is usually benign and of short duration but rhabdomyolysis with myglobinaemia, myoglobinuria and renal failure has been described in some adult cases (Holt and Kibblewhite, 1995).

Other renal complications

Jensen, (1967) reviewed 10 reports of influenza as an aetiologic factor in nephritis. Several anatomico-clinical forms have been described including: acute interstitial nephritis, acute exacerbation of a chronic nephropathy, an indirect acute diffuse glomerulonephritis, and Goodpasture syndrome. Some of the studies reviewed reported kidney involvement in at least 84% cases.

Influenza has also been reported as a cause of renal transplant rejection. Briggs *et al.*, 1972 described an outbreak of influenza A in a renal transplant unit. Five patients had proved episodes of infection and this coincided with episodes of acute transplant rejection in three. David *et al.*, 1972 reported 3 cases in whom there was an association between viral infection and transplant rejection. Two of these patients had serological evidence of influenza but one patient had received influenza vaccine one month prior to the rejection episode.

Toxic shock syndrome

Toxic shock syndrome (TSS) is a potentially fatal multi-system illness associated with *Staphylococcus aureus* infection and production of toxins first described in a group of children in 1978. The syndrome is characterised by fever, hypotension and erythroderma followed by desquamation. The largest series of patients with TSS complicating influenza or influenza-like illness was reported by MacDonald *et al.*, (1987). They described 9 cases of severe hypotension or death compatible with TSS during an epidemic of influenza in Minnesota. Four of the patients had influenza B, and *Staphylococcus aureus* was cultured from two individuals. Tolan (1993) reported a child with influenza A infection complicated by TSS. *Staphylococcus aureus* was cultured from the left nostril. The patient recovered with medical treatment. Tolan (1993) also reviewed seven reports containing 14 patients with TSS associated

with influenza and found that the mortality rate among reported cases was 43%.

Reye's syndrome

Reye's syndrome first described in 1963 is now a recognised complication of influenza B, and less commonly influenza A infection with an incidence of 1 - 6 cases per million children less than 16 years of age (Glasgow and Moore, 1993). Clustering of cases during the winter months has been associated with epidemics of influenza A and B and salicylate use (Corey *et al.*, 1976; Centres for Disease Control and Prevention, 1979; Waldman *et al.*, 1982). A particularly well documented clustering occurred during February and March 1974 when 316 cases were reported to the Centre for Disease Control. Surveillance for influenza indicated that clustering correlated both temporally and geographically with outbreaks of influenza B (Corey *et al.*, 1976). Clustering also occurred in 1978 - 79 when 85 cases were reported in association with influenza A (H1N1) (Centres for Disease Control and Prevention, 1979). There is also a strong epidemiologic link between salicylate usage and Reye's syndrome (Waldman *et al.*, 1982) and, possibly because of reduced salicylate usage, recent trends indicate a decreased incidence of cases (Hall, 1990).

The pathogenesis of Reye's syndrome remains uncertain but several mechanisms have been postulated. Liver biopsy in the acute phase shows swollen and pleomorphic mitochondria. Although the insult that initiates mitochondrial dysfunction is unknown, beta-oxidation is apparently blocked at multiple sites. Short and medium chain acyl CoA esters, which sequester free coenzyme A, accumulate within mitochondria. This reduces energy production and ATP within the mitochondria, which may prevent proper processing of imported protoenzymes and assembly of holoenzyme complexes on the inner membrane. Consequently catalytic activities fall and

many intermediary pathways including ureagenesis and gluconeogenesis are disturbed (Glasgow and Moore, 1993).

Otitis media

Markedly increased rates of acute otitis media (AOM) have been noted during epidemics of respiratory viruses including influenza. Heikkinen *et al.*, (1993) noted an attack rate for otitis media of 67% in young children infected with influenza type A. Recently, Buckman *et al.*, (1995) studied the role of influenza A virus in the pathogenesis of AOM. They inoculated 27 adults intranasaly with influenza A virus. All subjects became infected with the challenge virus. By day 4, 16 (59%) developed middle ear pressure of –100 H_2O or less and 4 of the 16 patients developed otitis media. One subject required myringotomy for pain relief. Middle ear effusion cultures were negative. However, for the subject who required myringotomy middle ear effusion and nasal washes were positive by PCR analysis for influenza A and *S. pneumoniae.* These findings indicate that otitis media during influenza infection is possibly mediated by middle ear underpressures and viral and bacterial infection.

Influenza during pregnancy

A relationship has been shown in many studies between maternal influenza and the subsequent development of schizophrenia in offspring, but remains controversial.(Wright and Murrary, 1993; Takei *et al.*, 1994; Kunugi H *et al.*, 1995). It has been suggested that viral infections occurring early in life may protect against atopy and asthma by deriving T helper cells towards a predominantly T helper 1 (Th1) phenotype (Martinez *et al.*, 1994). The selection of the appropriate T-cell population is an antigen driven process that occurs during the early stages of the immune response in the naive host. Th1 cells produce interferon gamma and interleukin 2 (IL-2) whereas T helper 2

(Th2) cells produce IL-4, and IL-10. IL-4 is one of the necessary signals that induce B cell clones to switch from IgM-producing to IgE-producing cells. Interferon on the other hand is a potent inhibitor of IgE production by B cells. In a similar fashion, Grange *et al.*, (1995) hypothesise that maternal antibodies and cytokines such as interferon might modify the infant's response, even to establishment of normal flora, in a way that could predetermine the pattern of T cell response for life. Their hypothesis gains support from the recent evidence showing that autoantibodies to the 60kDa human heat-shock proteins (neuroblastoma proteins of molecular weight 60kDa) are found in patients with schizophrenia (Kilidireas *et al.*, 1992) and the alleviation of schizophrenia symptoms by repeated injections of influenza vaccine (Lieberman and Craven, 1990). It is important, however, to emphasise that these hypotheses remain unproven.

An association between maternal mortality and influenza has been an observation for a long time. Deaths due to puerperal septicaemia and other acute complications of pregnancy showed influenza-related excesses in 1931 and earlier (Collins, 1957). Ashley *et al.* (1991) compared cause of death among a 1 in 15 random sample of deaths that occurred during the 1989/90 epidemic with deaths occurring during the same period in 1985/86. Analysis revealed a four-fold increase in deaths associated with pregnancy during the 1989/90 epidemic.

Further evidence in support of such an association may be found in several clinical studies. A study of influenza-related deaths in Boston revealed that 4 of the 32 deaths occurred in pregnant women. Of these 4 women, 3 were in good health; one, however, also had myasthenia gravis (Martin *et al.* 1959). In another report of 139 fatal influenza cases reported from New York State Health Department in 1957, 6 occurred in pregnant women (Communicable Disease Centre, Influenza surveillance report 26, 1957). In a series reported by Oswald *et al.*, (1958) seven of 379 patients with

influenzal pneumonia were pregnant two of whom died; one had mitral stenosis in addition. From this small sample it appears that most of the deaths during pregnancy occur in women without a known chronic medical risk factor.

4.4 Socio-economic impact of human influenza

Influenza outbreaks impose an enormous burden in terms of productivity and economic costs. In the United States it has been estimated that from 1971-72 through 1977-78 influenza resulted in 15 million days of work loss each year (Riddiough, 1983). During that period, annual expenditures to treat influenza and its complications averaged about $300 million (Riddiough, 1983). In the UK. during the 1957 epidemic the number of new claims for national insurance sickness benefits was about 2.5 million more than average for the same periods during the previous 5 years (Woodall *et al.*, 1958).

Influenza epidemics are also regularly associated with increased number of hospital admissions mostly from exacerbations of pre-existing chronic medical conditions. In the United States it is estimated that influenza epidemics are associated with more than 170,000 excess hospitalisations annually (Barker, 1986). During the 3 influenza seasons 1978/79, 1979/80, and 1980/81, Perrotta *et al.*, (1985) found that the highest rates of acute respiratory disease (*ICD-9-CM* codes 460 - 487) hospitalisations occurred among infants and persons aged 65 years or older. However, the rates of hospitalisation for adults 45 - 64 years and pre-school children aged 1 - 4 years were greater than 1 per 1000 persons. During the 1978 influenza epidemic in Holland it was estimated that one out of every 1300 patients with diabetes mellitus was hospitalised because of pneumonia and one of every 260 patients with IDDM was hospitalised for diabetic ketoacidosis (Bouter, 1991). In Leicestershire, during the 1989-90 epidemic hospitalisations for acute respiratory conditions increased by 42% when compared with the mean

number of admissions during the corresponding period in 1987/88, 1988/89 and 1990/91 (data from Leicestershire Health Authority's Patient Administration System).

In addition to the enormous morbidity that accompanies epidemic influenza, substantial mortality is also associated with such outbreaks. In the United States it has been estimated that from 1971-72 through 1977-78 influenza resulted, on average, in 16,000 excess deaths annually (Riddiough, 1983). Total influenza-associated excess mortality in six epidemics from the winter of 1972/73 to 1980/81 was about 200,000. In England and Wales about 120,000 excess deaths were attributed to influenza during the ten winters after influenza A/Hong Kong (H3N2) first arrived in 1968/69 (Tillett, 1983); but none were recognised in the winters of 1978/79 to 1984/85 (Chakraverty, 1986). The 1989/90 epidemic was the worst to have hit Britain since 1975/76 causing almost 30,000 excess deaths. Only 10% of these were attributed to influenza, 20% to pneumonia, 19% to other respiratory causes, and the rest to circulatory and other causes (Ashley *et al.*, 1991). Thus influenza is responsible for many 'hidden' deaths.

4.5 Risk factors for fatal influenza

The risk factors for fatal influenza include chronic illness and residential care. In people aged 45 or more the presence of chronic medical disease increased death rates from pneumonia and influenza by 39-fold; cardiovascular, pulmonary, combined cardiovascular and diabetes, and combined cardiovascular and pulmonary disease increased the risk by 104-fold, 240-fold, 481-fold, and 870-fold respectively (Barker *et al.* 1982). In the United States, mortality studies during influenza epidemics revealed the presence of chronic ill health in 11 of 12 persons aged 45 to 64 years of age and 25 of 26 people aged over 65 who died from influenza or pneumonia (Barker *et al.* 1982). For previously fit individuals aged 65 years and over the

mortality rate from 'influenza' and pneumonia during the epidemic period was 9 per 100 000 (Barker *et al.* 1982). For residential patients with pulmonary disease and cardiovascular disease the death rate from influenza increased by 27-fold and 31-fold respectively over non residential patients with the same conditions (Nguyen-Van-Tam and Nicholson, 1992).

Several studies have shown increased mortality in diabetics during influenza epidemics. Endocrine deaths (mostly diabetic) increased by about 30% in the UK. during the 1989/90 epidemic, as compared to 1985/86 (Ashley *et al.*, 1991). In another study older onset diabetics were found to be 1.7 times more likely to die from pneumonia and influenza as compared with the general population (Moss *et al.*, 1991). Bouter *et al.*, (1991) found that the estimated relative risk of death among hospitalised diabetics rose by almost three fold during two epidemic years: 1976 and 1978 when compared to non-epidemic years: 1977 and 1979. Admissions for ketoacidosis rose by 50% during 1978, and mortality due to ketoacidosis was significantly higher during that period when compared with non-epidemic years (25.4% *vs* 14.6%; $p < 0.05$).

Patients with renal disease are possibly at increased risk of dying during influenza epidemics. Eickhoff *et al.*, (1961) has shown that among 86,000 excess deaths that occurred during influenza epidemics in the united States in the years 1957 to 1960, about 44,000 occurred in individuals with cardiovascular-renal disease. However they used a broad definition including all diseases of the heart, vascular diseases of the kidney and central nervous system, as well as diseases of the remainder of the vascular tree.

The risks of serious complications and death associated with influenza among persons infected with human immunodeficiency virus (HIV) and those with the acquired immunodeficiency syndrome (AIDS) have not yet been determined. Persons infected with HIV are clearly at increased risk for serious pulmonary infections caused by the same bacterial pathogens that

have been associated with influenza: *Streptococcus pneumoniae and Haemophilus influenzae*, and a recent report from the USA indicated that the number and percentage of deaths attributable to pneumonia and influenza among persons 25 to 44 years of age have more than doubled during the 1980s in cities with a high incidence of AIDS (Centres for disease control, United States. MMWR 1988). The peak of these deaths occurred during the winter, the season in which most deaths associated with influenza and pneumonia occur (Centres for disease control, United States. MMWR 1988).

CHAPTER 5

Influenza prevention

5.1 Influenza vaccine

The discovery by Burnet in 1936 that influenza virus could be grown in embyonated hens' eggs allowed the development of inactivated virus vaccine (Burnet, 1936). The vaccine was first developed during the late 1940s and remains the mainstay for protection against influenza. Early whole virus vaccines contained intact, formalin-inactivated virus and were associated with local and systemic reactions. Subvirion and split-product vaccines have largely replaced whole virus vaccines and are widely available. Current influenza vaccines are usually trivalent, containing two influenza A subtypes, H3N2, H1N1, and influenza B. The antigenic composition of the vaccine is reviewed annually and depends on the strains prevalent in the community. The only contraindication to vaccination is hypersensitivity to hens' eggs in which the vaccine virus is grown.

5.2 Recommendations for vaccine use

Vaccination is not recommended for the attempted control of influenza; rather it is considered for individuals at risk of developing influenza complications and death. These have been identified from mortality statistics dating back to the nineteenth century (Parsons, 1891; Eickhoff *et al.*, 1961). More recent studies adopted an approach quantifying the risk of dying from influenza with respect to presence of chronic medical conditions or residential status (Barker and Mullooly, 1982; Nguyen-Van-Tam and Nicholson, 1992).

In Great Britain the Department of Health, the Welsh office, and the Scottish Home and Health Department issue annual guidelines for influenza immunisation. In recent years influenza vaccine has been strongly recommended for adults and children with chronic pulmonary disease

including asthma, chronic heart disease, chronic renal failure, diabetes mellitus and other endocrine disorders, and conditions involving immunosuppression due to disease or treatment; and for people who live in residential care and other long stay facilities where rapid spread may follow the introduction of infection (Department of Health. Immunisation against infectious diseases 1992). Recommendations in other countries are similar with many also advocating immunisation of all individuals above 65 years of age (Nicholson *et al.*, 1995).

5.3 Vaccine up-take

In Great Britain influenza vaccine up-take among high-risk individuals is unacceptably low. In 1986, a study of patients with serious long-term cardiac disease, showed that only 17% had received influenza vaccine (Kurinczuk and Nicholson, 1989). A survey of general practices in Trent health region indicated that only 19.5% of the elderly had been immunised against influenza (Nicholson *et al.*, 1987). During the influenza epidemic which followed in 1989/90 there were 29,000 excess deaths in Great Britain almost exclusively in elderly individuals (Ashley *et al.*, 1991). In Leicestershire, during the epidemic, the immunisation rate in those who died from influenza was 24% (10 of 42) but 93% (39 of 42) of those who died had indications for the vaccine (Nguyen-Van-Tam and Nicholson, 1992). During the same epidemic the immunisation rate among asthmatics in Leicestershire was only 15% (Wiselka *et al.*, 1992).

A survey of general practices conducted in England during 1992 revealed that 89% had an agreed policy for influenza immunisation (Nguyen-Van-Tam and Nicholson, 1993). However, medical practitioners' policies and practices seem to have had only a modest effect on vaccine uptake since the last epidemic in 1989/90. A survey carried out in Leicestershire during 1992 indicated that among patients with either chronic cardiovascular or

respiratory disease, or diabetes, only 41% received vaccine (Nguyen-Van-Tam and Nicholson, 1993).

In a survey of 477 consultant geriatricians in the UK., 385 (81%) never offered influenza vaccine to patients in continuing-care wards. Of the 385, 216 (56%) felt that its use was inappropriate and 162 (42%) regarded it as unnecessary. Ineffectiveness was given as a reason for non-use by 128 consultants (33%) while 36 (9%) felt that it was too expensive for 'blanket' use. Forty-six (12%) were concerned that the vaccine might be harmful to their patients (Lennox *et al.*, 1990).

Clearly influenza vaccine uptake among 'high-risk' individuals is sub-optimal and efforts to improve vaccine uptake among high-risk individuals should address issues of vaccine efficacy and safety, and promote better vaccine delivery through primary care and hospitals.

5.4 Vaccine safety

Modern influenza vaccines are associated with minimal side effects. Margolis *et al.*, (1990) reported a randomised, double-blind, placebo-controlled, cross-over study comparing the frequency of adverse reactions following administration of trivalent split-antigen vaccine and saline placebo in 336 subjects 65 years of age or over. There was no significant difference between vaccine and placebo with respect to proportion of subjects reporting symptoms such as: fever, cough, coryza, fatigue, malaise, myalgia, headache, or nausea. However, a higher proportion of subjects reported post injection arm soreness after vaccine as compared with placebo (20.1% *vs* 4.9%).

During the 1976 National Immunisation Program in the USA 45 million individuals received swine influenza vaccine. During the first 4 weeks after vaccination more cases of Guillain-Barré syndrome were observed among vaccinees than among individuals who did not receive vaccine (Centres for Disease Control and Prevention. MMWR, 1977). The

estimated risk of acquiring Guillain-Barré during the vaccination program was 1 in 127,000 vaccinations with a mortality rate among cases of 4%. Since 1976 there has been no overall increase in frequency of Guillain-Barré syndrome among vaccine recipients, although there may have been a small increase in Guillain-Barré cases in vaccinated persons 18 - 64 years of age in the 1990/91 vaccine season (Centres for Disease Control and Prevention. MMWR, 1993). In contrast to the swine influenza vaccine, the epidemiologic features of the possible association of the 1990/91 vaccine with Guillain-Barré were not as convincing (Centres for Disease Control and Prevention. MMWR, 1993).

Vaccine safety in patients with renal disease

Administration of influenza vaccine to patients with renal disease is not associated with recurrence of immunologically induced glomerular disease. Pabico *et al.*, (1974) measured creatinine clearance and urinary protein excretion in 21 patients with glomerulonephropathies (17 with glomerulonephritis, 2 with renal amyloidosis, 1 with lupus glomerulonephritis, and 1 with diabetic glomerulosclerosis), before vaccination and weekly for 4 - 6 weeks afterwards. Creatinine clearance remained relatively unchanged in all patients. Minimal transient increase in proteinuria occurred in 5 (42%) patients with nephrotic syndrome two of whom were in remission.

Vaccination does not affect renal function or cause rejection among transplant recipients. Pabico *et al.*, (1976) measured creatinine clearance and urinary protein excretion, before and weekly for 4 - 8 weeks after vaccination, in 30 renal transplant patients. The variation in weekly creatinine clearance values post-vaccination were not significant when compared with pre-vaccination values. After vaccination minimal and transient changes in protein excretion were observed but they were not statistically different from

pre-vaccination values. Carroll *et al.*, (1974) followed 25 renal transplant patients for 12 months after vaccination. No rejection episodes were observed. Kumar *et al.* (1978) followed 20 renal transplant patients for 5 months after vaccination. No change in renal function occurred except in one patient who was experiencing a slow chronic rejection prior to vaccination; this continued at the same rate of progression.

Vaccine safety in patients infected with the Human Immunodeficiency Virus

The effect of influenza immunisation in HIV-infected individuals has focused on lymphocyte counts and serum p24 antigen levels before and after vaccination. Several studies have revealed no adverse effect of vaccination on immune function or symptoms. Huang *et al.*, (1987) measured lymphocyte numbers before and after immunisation of 35 HIV-infected homosexual men (10 asymptomatic, 25 with persistent generalised lymphadenopathy) before and 4 - 6 weeks after vaccination. The mean numbers of lymphocytes, T-cell subsets, and T-helper to T-suppresser cell ratios, as well as clinical status remained stable. Nelson *et al.*, (1988) measured serum p24 antigen levels in 54 HIV seropositive persons, before and after vaccination. No increase in the prevalence or level of serum HIV p24 antigen or clinical deterioration was detected one month after immunisation. Miotti *et al.* (1989) found no statistically significant changes in p24 levels 8 weeks after vaccination in 78 HIV seropositive men. It is, however, important to note that these were uncontrolled studies and the period of follow up was short (4 - 8 weeks).

Recently, O'Brien *et al.*, (1995) studied the effect of influenza vaccination on HIV replication in peripheral blood mononuclear cells (PBMCs) from 20 HIV-1 positive vaccinees, and 14 HIV-1 positive controls who did not receive vaccine. The study subjects were at an intermediate stage of HIV disease at entry to the study with no AIDS defining illnesses.

Using quantitative polymerase chain reaction, they showed that during the two-month study period there was little change in levels of proviral DNA in PBMCs. However, there was a significant relative increase in post vaccination HIV-1 RNA level in PBMC from the 20 patients who received the vaccine (11.6- ± 5.0-fold increase; $p < 0.002$). Greater than four-fold increase were seen in 10 (50%) of vaccinated subjects. The peak HIV-1 RNA levels typically occurred at 1 or 2 weeks post-vaccination and returned to baseline at latter time points during the 4 to 6 weeks follow-up period indicating that HIV-1 RNA induction is transient.

Vaccine safety in patients with asthma

The weight of the available evidence indicate that influenza vaccine does not exacerbate asthma, but conflicting reports exist. Bronchoprovocation tests have revealed increased bronchial reactivity in asthmatics given influenza vaccine. Ouellette and Reed (1965) measured FEV1 and maximum expiratory flow rate (MEFR) before and after methacholine aerosol in 10 asthmatics and 10 normal subjects for 6 days before vaccination with a polyvalent influenza vaccine and 4 days afterwards. Neither group showed any significant change in pre-methacholine FEV1 or MEFR during the study. However, following vaccination, the mean change in FEV1 after methacholine among those with asthma was 42% compared with a mean change of 24.7% for the 6-day control period. Statistical analysis showed that the increase in the percent change in FEV1 one day after vaccine was significant ($p < 0.001$). The effect of vaccine lasted for 72 hours. None of the patients had respiratory symptoms. Similar findings were noted with methacholine by Anand *et al.*, (1968) in 11 of 24 patients with asthma of known and unknown origin. The changes were noted within 8 hours of immunisation and persisted for up to 72 hours. As before there was no effect on the pre-methacholine FEV1. Increased bronchial

reactivity following influenza vaccine has also been demonstrated with histamine (Banks *et al.*, 1985).

There have been few placebo-controlled studies of symptoms and/or routine pulmonary function tests following immunisation. Stenius-Aarniala *et al.* (1986) assessed the effects of immunisation with killed bi-valent split-product influenza virus vaccine by comparison with placebo in a double-blind study of 318 adult patients with chronic asthma. No difference was observed in peak expiratory flow rate (PEFR) or in symptoms of bronchial obstruction between the groups during the first week after immunisation. Similar findings were reported by Kava *et al.*, (1987) in 27 asthmatics given vaccine or placebo. In a placebo-controlled, cross-over study, Campbell and Edwards (1984) gave tri-valent vaccine to 28 patients and measured the best of three PEFR in the morning and evening for one week after each injection. The evening PEFR decreased significantly (by a mean of 168L/min over the whole week) and there was a non-significant reduction in the morning PEFR (by a mean of 45L/min).

Bell *et al.* (1976) studied 79 asthmatic children. They compared PEFRs of vaccinees with non-vaccinees, or those immunised two weeks previously and noted that there was a slight decrease in morning PEFR between 24 to 48 hours after immunisation. A maximum drop of approximately 12% in PEFR was recorded at 48 hours; this was, however, statistically significant. There was also an increase of approximately 0.4 in mean daily count of aerosol therapy with brochodilators per patient at 48 hours after immunisation. However, the same investigators were unable to detect any changes in FEV1, or maximum mid expiratory flow when pre- and post-vaccination pulmonary function data for 47 young asthmatic subjects were compared (Bell *et al.*, 1977). Similarly Albazzaz *et al.*, (1987) gave 14 asthmatic adults a trivalent subunit vaccine and found no significant changes in symptoms of asthma, use of bronchodilator drugs, or PEFRs 7 days before and 14 days after

vaccination, or the amount of histamine required for a 20% fall in forced expiratory volume in one second. Kava and Laitenen, (1985) found that conductance fell significantly 3 days after vaccination of 14 adults with asthma, but several subjects had upper respiratory tract symptoms and a common cold may have been responsible for the observed effect.

Vaccine safety in patients with systemic lupus erythematosus

Influenza vaccines are not associated with adverse effects on underlying disease activity in patients with systemic lupus erythematosus (SLE). Ristow *et al.*, (1978) studied the effect of monovalent influenza A vaccine by a case control study in 29 patients with SLE and 29 healthy controls matched for age and pre-vaccination antibody titre. Each patient had clinical and laboratory evaluation before and 4 and 8 weeks after immunisation. Laboratory evaluation included measurement of erythrocyte sedimentation rate, blood count, total haemolytic complement (CH_{50}), third (C3) and fourth (C4) component complement levels, level of antibody to double-stranded DNA, creatinine clearance and urinary protein excretion. Except for one patient with active lupus erythematosus, who developed renal disease, there was no evidence of an increase in lupus erythematosus activity after immunisation.

Similar findings were recorded by Williams *et al.*, (1978) from a double-blind placebo-controlled study of bivalent influenza vaccine in 40 patients with SLE. Patients were followed for 20 weeks during which one patient in the vaccine group developed patchy alopecia and arthritis 4 months after immunisation. In the group as a whole, haemoglobin values, sedimentation rates, renal function, C3 and DNA binding values were unchanged. Brodman *et al.*, (1978) in a case-control study including 46 SLE patients and 58 healthy controls found that symptoms after immunisation and boosting with monovalent influenza A vaccines were somewhat more frequent in patients than in healthy controls; however all symptoms were minor and no major

flare of illness occurred. There was no significant induction or increase of pre-existing autoantibodies among patients after vaccination. Louie *et al.*, (1978) in a case-control study followed 11 patients with SLE and 8 healthy controls for three months after immunisation with whole bivalent influenza A vaccine. Only one patient with SLE developed diffuse proliferative glomerulonephritis. The remaining patients (10 in total) showed no change in clinical organ involvement.

Vaccine safety in patients with multiple sclerosis

Sibley *et al.*, (1976) investigated in a retrospective study the effect of influenza vaccine in 93 patients with multiple sclerosis (MS). The patients received a total of 209 doses of vaccine. Retrobulbar neuritis developed 24 hours after the second dose of vaccine in a woman who had frequent attacks of MS during the three years before vaccination. None of the other patients had new symptoms or signs suggestive of new central nervous system lesions. The same authors investigated the effect of bivalent influenza A vaccine (Victoria A-New Jersey A) in 65 patients with MS; sixty two patients with MS, who were reasonably well-matched did not receive vaccine and were used as controls (Bamford *et al.*, 1978). The patients and controls were followed up for two months. One vaccinee developed a neurologic symptom and another had increased severity of a prexsisting dysfunction. Two of the 62 controls experienced new neurologic symptoms, and two others noted an increase in the rate of disability. Recently, Salvetti *et al.*, (1995) investigated the effect of killed influenza vaccine on disease activity in MS patients. They evaluated 6 patients during the year before and the year following vaccination. Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) was performed one day before and at days 15 and 45 after vaccination. Cumulatively, patients experienced fewer relapses in the follow-up period after vaccination than during the year before (2 *vs* 6). Comparing the expanded disability

status scale (EDSS) variation during the two periods, in five patients the disease did not appear to progress faster after vaccination than before. However, one patient experienced an EDSS increase of 2.0 and a shift to progressive form of disease in the post vaccination year as opposed to an increase of 1 during the year before. This was the only patient who developed a new contrast-enhanced lesion at Gd-MRI on day 15. The same patient presented the highest number of lesions and total lesion area at baseline Gd-MRI and the authors conclude that influenza vaccine should be used with caution in patients with active/progressing disease.

Vaccine safety in patients taking theophylline and warfarin

Renton *et al.*, (1980) observed that theophylline metabolism was decreased by influenza vaccination. They suggested that the reduced elimination and increased serum levels of aminophylline were due to decreased cytochrome P-450 activity. Subsequently, Kramer and McClain, (1981) investigated the effect of influenza vaccination on hepatic drug metabolism with use of the [^{14}C] aminopyrine breath test, an indirect but sensitive and reproducible measure of hepatic cytochrome P-450-mediated drug metabolism activity. In a case-control study in healthy volunteers they demonstrated marked depression of aminopyrine metabolism one week after influenza vaccination. They also claimed that vaccination may have resulted in activation of warfarin, which is metabolised by the cytochrome P-450 enzyme system, in a patient ten days after immunisation resulting in massive upper-gastrointestinal-tract bleeding and prolonged prothrombin time. However, three subsequent studies failed to support these initial observations. A prospective study of residents in 52 nursing homes (155 taking theophylline, 48 taking warfarin) during the 1982/83 season failed to reveal evidence of warfarin or theophylline toxicity in the 30-day period after vaccination (Patriarca *et al.*, 1983). Another study in 41 adult patients who were receiving

warfarin showed no statistically significant change in prothrombin time between base line and days 3, 7, and 14 after vaccination. Also there were no major or minor bleeding episodes after vaccination (Raj *et al.*, 1995). A study of theophylline pharmacokinetics in 16 normal subjects showed no significant change in half-life, total body clearance, volume of distribution or maximal serum theophylline concentration compared with pre-vaccine values at either 2 or 6 days after vaccination (Hannan *et al.*, 1988).

5.5 False antibody responses following vaccination

Recently influenza vaccination was associated with multiple false positive viral enzyme-linked immunosorbent assays (ELISAs) for human immunodeficiency virus (HIV), human T-cell lymphotrophic virus type 1 (HTLV-1), and hepatitis C virus (Mackenzie *et al..*, 1992). This response occurred in 0.6 - 1.7% of blood donors who received influenza vaccination. It appeared to be of relatively short duration, mean 75 days, for HIV and HTLV-1, but may persist longer for hepatitis C virus. It is believed that this false positive reaction is caused by an early non specific IgM response after vaccination (Mackenzie *et al.*, 1992)

5.6 Chemoprophylaxis

Amantadine (1-aminoadamantane) and its analogue rimantadine (a-methyl-1-adamantane methylamine) are both effective when used as prophylaxis against influenza A infection (Dolin *et al.*,1982). Amantadine and rimantadine inhibit H1N1, H2N2, and H3N2 strains of influenza type A including 'new' epidemic strains, so it is to be expected that future variants, including pandemic strains, will be similarly inhibited (Hayden *et al.*, 1980). Their level of efficacy when used as prophylaxis is estimated to be in excess of 80% in young and healthy individuals, similar to that of vaccine (Dolin *et al.*, 1982), and protection may be additive to that of vaccine.

Currently only amantadine is licensed for use in the United Kingdom. Amantadine is almost completely absorbed after oral administration, does not undergo metabolic changes and is excreted unchanged by the kidneys with a half life of 12 - 18 hours. Because of reduced clearance in the elderly and patients with reduced renal function, care should be taken to ensure that the drug does not accumulate to toxic levels in these two groups. Minor neurological symptoms including insomnia, lightheadedness, difficulty in concentration, nervousness, dizziness, and headaches develop in 20% of individuals receiving 200 mg daily (Bryson *et al.*, 1980). Amantadine is contraindicated in epilepsy and gastric ulceration, and should be used cautiously in patients with cardiovascular disease, renal disorders, or with cerebral atherosclerosis. Drug resistant strains of influenza A are being recovered increasingly from humans undergoing therapy or prophylaxis with amantadine or rimantadine in the setting when symptomatic cases are being treated (Belshe *et al.*, 1989).

Because of cost, requirements for prolonged administration, and potential side effects, mass prophylaxis of the general population is impractical. Chemoprophylaxis should be considered for high-risk individuals during an outbreak who have not yet received the vaccine, and can be given for two weeks, covering the period of greatest vulnerability, if vaccine is given simultaneously. Antivirals should also be considered throughout the influenza season, for those in whom vaccination is contra-indicated, or to supplement vaccine in individuals who are expected to respond poorly to vaccination because of disease or treatment e.g. the immunocompromised and patients with severely impaired renal function.

Although current antivirals are effective against influenza, their use has been limited by side effects and emergence of drug resistance. This has prompted research in developing new virus inhibitors which have improved potency and selectivity. Rational computer-assisted drug design has been

employed in developing two inhibitors of the enzyme neuraminidase, 4-amino- and 4-guanidino-Neu5Ac2en, which are active against both A and B viruses (von Itzstein *et al.*, 1993). Their efficacy has been established in cell culture and in animal models. 4-guanidino-Neu5Ac2en inhibited influenza A virus in cell culture at lower concentration than amantadine or rimantadine and inhibition was not affected by resistance to either drug (Woods *et al.*, 1993). At present trials are underway to determine the effectiveness of these new enzyme inhibitors in prevention or treatment of naturally occurring influenza in humans.

CHAPTER 6
Vaccine effectiveness

6.1 Introduction

The efficacy of influenza vaccine has been assessed by challenge studies, field trials, and study of the immune response. Challenge studies have been performed in healthy young volunteers with both wild and live-attenuated viruses. Bell *et al.*, (1957) conducted a placebo-controlled study in adult volunteers during an A/Asian epidemic. The virus was influenza A/Valley Forge/57, which was antigenically similar to the far east strain. Clinical illness developed in 18 out of 23 (78%) volunteers who received placebo. However, 14 of 32 (44%) volunteers who received A/Japan/305/57 (H2N2) vaccine developed influenza-like illness. Therefore, vaccination gave significant though incomplete protection. Goodeve *et al.*, (1983) conducted a placebo-controlled study in a group of volunteers who were inoculated with live-attenuated influenza B virus. Vaccinees were inoculated with sub-unit B/Hong Kong/73 vaccine containing 5, 10, 20, or 40 μg of HA. The incidence of infection by challenge virus was determined by HI antibody. The lowest incidence of infection was seen in volunteers given the highest dose of vaccine. However, all doses of vaccine induced some protection against challenge virus infection. Such design would, obviously, be unethical in the elderly and others at risk from influenza.

In field trials vaccinated and unvaccinated individuals are exposed to natural field pathogens, but this type of study faces many practical difficulties including the sporadic nature of influenza epidemics; the time of their occurrence is unpredictable; mismatch between vaccine strains and epidemic viruses; possible differences in exposure rates of compared groups; possible clinical misdiagnoses of cases; and ethical problems in the elderly, and people with chronic ill-health for whom vaccination is recommended. As a result

most of the studies dealing with influenza vaccine efficacy in 'high-risk' groups have been retrospective.

6.2 Immune response studies

The immune response study determines the response to vaccination by measuring serum antibody against the haemagglutinin glycoprotein of influenza virus as this was found to be a predictor of protection against infection (Goodeve *et al.*, 1983; Davies and Grilli, 1989). Analysis of the contribution of serum antibody reveals that serum HI of 1:40 or greater is associated with protection against infection; HI of 1:20 or 1:10 are associated with lesser degree of protection (Wenzel et al., 1973; Kilbourne et al., 1973). Serological response may be expressed using one or more of the following parameters: (1) the mean fold increase, i.e., the anti-logarithm of the difference between the logarithm of mean titres of post and pre-vaccination sera; (2) the protection rate, i.e., the proportion of subjects exceeding a given protection threshold after vaccination; (3) the response rate, i.e., the proportion of subjects who show at least fourfold titre increase after vaccination.

Antibody production following influenza vaccination may be influenced by several factors including: quantity of antigen inoculated, history of exposure to various influenza antigens either from naturally acquired infection or vaccination, age, and health state of subjects studied and medications taken at the time of the study.

The effect of quantity of antigen on the immune response

Several studies have shown a graded relationship between the quantity of antigen inoculated and antibody response. The Pandemic Working Group of the MRC Committee on Influenza Vaccine and other Respiratory Viruses (1977) gave graded doses of whole virus vaccine containing the newly

emerged strain A/New Jersey/76 (H1N1) to groups of volunteers. Those who were seronegative to the virus before immunisation showed a post vaccination geometric mean antibody titre ranging from 64 to 148 with an increase in vaccine dose from 8 to 61 μg haemagglutinin. For those with pre-existing antibody against H1, there was a 7 to 36 increase in geometric mean antibody-titre with increases in haemagglutinin from 4 to 61 μg. Similar results were reported by Nicholson *et al.*, (1979) using sub-unit A/USSR/77 (H1N1) vaccine, and Goodeve *et al.*, (1983) using sub-unit B/Hong Kong/73 vaccine.

However, vaccines that contain large dose of haemagglutinin are reactogenic. Doses of 61 μg haemagglutinin of whole virus vaccine caused systemic reactions in over 60% of vacinees whereas doses of 18 - 27 μg haemagglutinin caused systemic reactions in 40% (Pandemic Working Group of the MRC Committee on Influenza Vaccine and other Respiratory Viruses, 1977). Similar results are reported with sub-unit vaccines. Doses of 40 μg sub-unit B/Hong Kong/73 vaccine caused local reactions in 24% of vaccinees whereas doses of 5 μg haemagglutinin caused local reaction in only 9%. For those who were given 20 and 10 μg haemagglutinin reactions occurred in 19% and 11% respectively (Goodeve *et al.*, 1983). Furthermore the dose response effect plateaus with higher doses of antigen and simply increasing serum haemagglutination inhibition titres does not necessarily increase protection (Goodeve *et al.*, 1983).

The effect of previous exposure to influenza antigens

Because the haemagglutinin and neuraminidase molecules of different influenza A viruse subtypes share antigenic determinants, yet also possess subtype or strain specific determinants as well, the secondary response during re-infection or after immunisation comprises two coincident responses: (a) secondary response to the common antigenic determinants and

(b) primary response to epitopes of the virus not previously encountered. The imprinting of the initial challenge (original antigenic sin) determines thereafter the nature of the antibody response to heterotypic infection or immunisation with future antigenic variants. Masurel *et al.*, (1981) analysed sera from 378 children and young adults immunised with whole virus vaccine containing 10, 20, or 40 μg HA of A/USSR/92/77 (H1N1) influenza virus. A booster immunisation was administered 6 weeks later with 20 μg HA of the same virus. Many of the participants had been immunised during the two preceding years with a whole virus vaccine containing A/New Jersey/8/76 (H1N1). After booster immunisation with A/USSR/77 virus, participants showed a higher homologous antibody response if they had not been immunised with A/New Jersey/8/76 virus in previous years. After first dose and especially after booster immunisation with A/USSR/77 virus a high response against A/New Jersey/8/76 and adequate levels of A/New Jersey/8/76 antibody were found in participants who had been immunised previously with A/New Jersey/8/76 virus. Such response is not necessarily in the best interest of the host if during processing most antigen is preferentially bound by the expanded B cell population committed to the formation of antibody that is heterotypic rather than homotypic and therefore less relevant to the new experience. However, heterotypic antibody formed in the secondary response is sufficient in quantity so that among closely related variants cross immunity may provide sufficient protection (Couch *et al.*, 1979).

The effect of age on the immune response

Results of many studies indicate that the magnitude of serum haemagglutinin inhibition (HI) antibody produced in response to influenza vaccine is lower in older than in younger adults (Cate *et al.*, 1983; Feery *et al.*, 1979), although conflicting data exist (Iorio *et al.*, 1989). These observations can be partly

explained by pre-vaccination serum HI antibody and difference in health status of groups studied. It is also likely that some elderly individuals respond poorly to influenza vaccination due to age-related changes in the immune function. In mammalian species there is decline in immune function that begins at the time of sexual maturation and progresses through out life, and antibody production is known to decline with ageing (Makinodan and Kay, 1980). Beyer *et al.*, (1989) reviewed 17 papers that compared the anti-haemagglutinin IgG seroresponse following vaccination of young and elderly individuals. They found that, among 30 studies in which vaccine components could be studied independently, 10 showed better immune response in young subjects than elderly, 4 favoured results in the elderly, and 16 could not detect a significant difference between the two groups. However, nine of the 16 studies tended to favour young subjects, and two older ones.

The effect of health state of subjects vaccinated

Antibody production following vaccination may be reduced in subjects with illness affecting the immune system, and in those taking immunosuppressive therapy. Three groups of patients have been specifically studied in this respect:

Patients with chronic renal failure mount a poor antibody response following influenza vaccination. Cappel *et al.*, (1983) compared the immune response following vaccination of 40 haemodialysis patients with 33 patients with chronic bronchitis. Fewer patients responded to H3N2 and B/Hong-Kong viruses in the haemodialysis group as compared to those with chronic bronchitis. Similar results were reported by Versluis *et al.*, (1987) among 98 patients undergoing long term haemodialysis and 29 healthy controls.

The antibody response of patients infected with HIV following vaccination is lower than HIV-seronegative controls. Nelson *et al.*, (1988) studied 25 patients with AIDS, 14 patients with AIDS-related complex, 27

HIV-seropositive men with lymphadenopathy only, or no symptoms, and 38 HIV-seronegative controls (22 of whom were homosexual men). Protective levels (1:64 or greater) of haemagglutination inhibition antibodies were attained by 94% to 100% of HIV-seronegative controls, 52% to 89% of HIV-seropositive asymptomatic subjects, and 13% to 50 % of subjects with AIDS or AIDS-related complex. In a similar study Miotti *et al.*, (1989) used a two dose regimen of inactivated influenza vaccine. The two dose regimen induced protective haemagglutination inhibition-antibody to influenza A (H1N1) and (H3N2) virus less often in subjects with symptomatic HIV infection than in HIV-negative controls (39% *vs* 87% and 46% *vs* 97%, respectively).

Special attention should be paid to the timing of vaccine administration in patients receiving cytotoxic drugs. Studies in children and adults receiving cytotoxic agents showed that a significantly lower proportion of patients seroconverted (50% of adults and 37% of children) when vaccine was administered simultaneously with cancer chemotherapy than administration at the nadir of the white cell count response or when no chemotherapy was administered (Gross *et al.*, 1978; Ortbals *et al.*, 1977). Over 90% of children (68 of 74) and adults (13 of 14) seroconverted when cancer chemotherapy was not being used (Gross *et al.*, 1978; Ortbals *et al.*, 1977).

6.3 Protection studies

Early trials of inactivated influenza vaccine were carried out in young healthy individuals. Two approaches have been adopted in assessing an influenzal illness: (a) an assessment using laboratory data which were largely serological, and (b) a purely clinical assessment. Each approach suffers shortcomings which should be taken into consideration when interpreting results. When using serological methods the protection afforded can be over-estimated because immunised persons contracting influenza may show an insignificant fold-increase in antibody and thus be discounted; this drawback

was first described by McDonald and Andrews (1955). The drawback of trials where only clinical assessment is used is that dilution of cases of influenza infection by patients with non-influenza virus infection would result in a misclassification bias and diminish estimates of protection. However, when clinical trials are carried out during outbreaks with high attack-rates misclassification bias is usually minimal.

A field trial, conducted in 1957, included 3093 public schools boys and trainee teachers (Committee on Influenza and other Respiratory Virus Vaccines, 1958). Subjects were randomly allocated to an Asian influenza vaccine, a polyvalent vaccine from older (non-Asian) strains, and an influenza B vaccine. Reliance was placed mainly upon clinical assessment in diagnosing influenza. A substantial protective effect was afforded by the Asian vaccine after an interval of only eight days. The attack rate nine to 15 days after vaccination was only 8% (33/404) among those given the Asian vaccine whereas it was 25% (107/437) and 25% (106/429) in the other two groups. Similar results were obtained in trainee teachers, and the overall protection in the two groups was 67% and 75% respectively (Committee on Influenza and other Respiratory Vrus Vaccines, 1958).

Gundelfinger *et al.*, (1958) studied a population of 3355 military recruits in the USA. Subjects were randomly allocated to an Asian monovalent influenza vaccine (A/Japan/305-57), a polyvalent vaccine (A'/Swine A/FM1 and B/GL/1739-54), and a formalin-inactivated trivalent vaccine containing antigens of types 3, 4 and 7 adenoviruses. An epidemic similar to the Asian strain occurred in the autumn/winter of that season. During the period August 25 to September 9, the attack rate was 23.5/1000 per week in the monovalent vaccine group, 49.7/1000 per week in the polyvalent vaccine group, and 58.9/1000 per week in the formalin-inactivated trivalent adenoviruses vaccine group. Overall Asian monovalent vaccine effectiveness in preventing febrile respiratory illness, occurring two weeks or

more after inoculation, was 60%. Late in September and early October rates of respiratory illness showed a sharp increase in all populations in the study area; this was accompanied by the highest influenza virus isolates observed in the previous eight years. During this period, the effectiveness of Asian monovalent vaccine in reducing febrile respiratory illness was 83%. This exemplifies the aforementioned misclassification bias resulting in diminished estimates of protection that may occur during periods of low influenza activity.

Apparent failure of inactivated vaccine to protect against influenza in young individuals may be found in studies conducted at a boarding-school for boys (Hoskins *et al.*, 1973; 1976; 1979). A total of 800 pupils aged 11 to 19 took part in a series of studies of inactivated vaccine during outbreaks of influenza A (H3N2) during three seasons in 1972, 1974 and 1976. The cumulative confirmed-case rates in 375 boys who were in the school during all three outbreaks was 40 - 50% irrespective of their respective vaccinations with vaccines containing strains of H3N2 viruses (Hoskins *et al.*, 1979). The trials began in October, 1970 and those boys whose parents gave permission, were randomly allocated each year to receive influenza A or B vaccine with 'currently' formulated vaccine for that year. The first outbreak, due to A/England/72 virus, occurred in December 1972. At that time those who had received the A/Hong Kong/68 vaccine once, twice or thrice, experienced significant protection and the rate of virologically confirmed illness was 2.9% (11/384) compared with 9.4% (32/340) for those who received influenza B vaccine and 14.8% (13/88) for non-vaccinees (Hoskins *et al.*, 1973).

However, during the epidemics of 1974 and 1976 the picture was different. In the spring of 1974 an outbreak caused by a strain similar to A/Port Chambers occurred. There were no cases among 68 boys known to have been infected in the A/England/72 outbreak. The attack rate of influenza A/Port Chambers was significantly higher ($x^2 = 9.64$, $p < 0.005$)

among boys previously given the A/Hong Kong/68 vaccine (18%; 44/244) than in those given influenza B vaccine (8%; 18/226) (Hoskins *et al.*, 1976). The attack rate in boys who received A/England vaccine was low. Most of this group received vaccine for the first time and were well protected (4 cases in 125 boys). A small group who had previously received A/Hong Kong vaccine and were revaccinated with A/England vaccine experienced a rather higher attack rate (5 cases in 44 boys). However, a statistical re-analysis restricted to boys present in the school during outbreaks in 1972, 1974 and 1976 does not substantiate a lower attack rate in those vaccinated with A/ Port Chalmers vaccine for the first time compared to those vaccinated in 1974 and 1975, as suggested by the authors (Hoskins *et al.*, 1979).

The protection against influenza-like illness in the elderly is reported to be lower: a review of 16 studies in geriatric homes between 1972 and 1985 showed a mean protection against influenza like-illness of only 27% for influenza A (H3N2) vaccines (Arden *et al.*, 1986). Influenza B vaccines fared even worse, with a mean protection rate of 21% in seven studies (Arden *et al.*, 1986). Feery *et al.*, (1979) found no protection against virologically-proven cases of influenza A/Victoria/3/75 in elderly people in residential homes in Australia, but vaccinated subjects evidently had amelioration of illness severity as assessed by the attending medical officer.

Of greater relevance, however, are the reductions in morbidity and mortality achieved with vaccine. Howells *et al.*, (1975) assessed vaccine effectiveness in residents of old people's homes over three influenza seasons 1971 to 1974 inclusive. Significantly fewer vaccinees developed bronchopneumonia or died each year. Patriarca *et al.*, (1985) assessed vaccine effectiveness during the 1982/83 influenza A (H3N2) epidemic in seven nursing homes in USA. Unvaccinated residents were more likely to be hospitalised (Risk Ratio, 2.4; 95% CI, 1.6 - 5.3) or die (Risk Ratio, 5.6; 95% CI, 1.2 - 9.1). Gross *et al.*, (1988) studied vaccine efficacy in reducing mortality

among institutionalised patients. Mortality was significantly less among vaccinees when compared with those who did not receive vaccine (13/181 *vs* 22/124; p = 0.008) and vaccine efficacy in reducing mortality was estimated to be 59%.

Barker and Mullooly, (1980) reported a retrospective analysis of vaccine effectiveness in reducing pneumonia- and influenza-associated hospitalisations and mortality among non-institutionalised subjects aged 65 years or older. During the 1972/73 influenza A (H3N2) epidemic, vaccine derived from the A/Hong Kong/68 (H3N2) virus gave an estimated 72% (31% to 100%) reduction in hospitalisation and 87% (52% to 100%) reduction in mortality. However, vaccine derived from the H2N2 subtype of influenza A virus failed to protect against the Hong Kong (H3N2) virus during the 1968/69 epidemic. A meta-analysis of 16 studies revealed reductions of 23% in morbidity (95% CI 6 - 37) and 67% in mortality (95% CI 53 - 76) (Strassburg *et al.* 1986). A review of seven studies by Nicholson, (1990) revealed reductions in the incidence of bronchopneumonia (49 - 90%; mean 69%), admissions to hospital (47 - 72%; mean 59%), and deaths (0 - 100; mean 69%). The shortcomings of such studies are well recognised: the majority involved residential care with no distinction between those with and without chronic diseases. They were also non-randomised, uncontrolled, observational studies and the possibility that vaccine was withheld from patients with poor quality of life, or that medical management of sick non-vaccinated subjects was different to vaccinees cannot be excluded. Clearly there is a need for a carefully designed study to investigate influenza vaccine effectiveness in the elderly and those at risk of developing influenza complications and death. The present studies were designed to address this issue.

METHODS

CHAPTER 7
Methods

7.1 Obtaining ethical approval

The Department of Public Health Medicine in Leicester initiated a retrospective review of General Practitioners' (GP) notes of patients dying with influenza during the 1989 - 90 epidemic to establish their vaccination status. Ethics committee approval was not considered necessary for this initial review and the results were subsequently published and formed the basis of a large case-control study.

For the current case-control study we obtained ethical approval from the Leicestershire Committee on the Ethics of Clinical Research Investigation. In addition to Leicester, the project involved 40 District Health Authorities (DHAs) covering six Health Regions in England. Two DHAs stated that ethical approval was not required for the proposed research. During the period December 1992 to July 1993 a letter was sent to the chairmen of 36 local research ethics committees (LRECs) covering the remaining 38 DHAs explaining the background leading to the proposed research, the aims and objectives of the project, and methods to be employed (Appendix I). A copy of the publication arising from the pilot study was included with the letter together with a copy of the questions to be addressed. We informed three chairmen that local ethical committee approval for this project was awaited. The remaining 33 chairmen were contacted after approval in Leicester was obtained. We asked whether ethical approval was required in addition to that obtained in Leicester and if so, for a copy of the application form.

7.2 Mortality study

The study was carried out between November 1992 and July 1994 in 36 District Health Authorities (DHAs) embracing five Health Regions in England and a resident population of about 10.5 million.

Study power

The study size provided a power in excess of 80% to detect an odds ratio of 0.7 (vaccine efficacy = 30%) at $p < 0.05$.

Identification of fatal influenza cases

Names and addresses of Directors of Public Health were obtained from *The Hospitals and Health Services Year Book, 1992* (The Institute of Health services Management, 1991). Of the 95 DHAs in England a letter was sent to the Directors of Public Health in 77 DHAs asking for their assistance in identifying deaths registered as 'influenza' anywhere on the death certificate during the period week 44, 1989 to week 8, 1990 (Appendix II). The letter explained that the 1989-90 epidemic was responsible for 26,000 deaths in England and Wales and that the Chief Medical Officer and his Influenza Advisory Committee were extremely concerned about the deaths and the low level of immunisation. It also explained that concerns about vaccine efficacy were voiced by general practitioners and patients but because influenza vaccines are licensed and recommended by the Department of Health it was deemed unethical to mount prospective double-blind placebo-controlled studies to test their efficacy; therefore alternative strategies such as case-control studies were considered. Directors of Public Health were told about the pilot study conducted in Leicester during the previous winter, and a copy of the publication arising from the study was enclosed with the letter; they were told that we intended to extend the pilot study and conduct a large case-control trial collecting data from the 1989 - 90 epidemic.

A total of 55 DHAs agreed to participate, 7 were unable to help, and 15 Directors of Public Health failed to respond. Fourteen of the 55 DHAs could not be included in the study as their FHSAs had not retained the notes of patients who died during the study period. Four additional FHSAs covering five Health Authorities were subsequently, i.e. after ethical committee approval, found to have destroyed their notes (Appendix III shows details of these DHAs). I visited each of the 36 DHAs where information was available, and identified all patients aged 16 years or over whose primary or contributory cause of death was ascribed to influenza during the period week 44, 1989 (4.11.89 inclusive) to week 8, 1990 (23.2.90 inclusive) by reviewing the death register held at each DHA. I obtained a photocopy of each death certificate.

Letters and photocopies of relevant death certificates were then sent to the General Managers of FHSAs covering the 36 DHAs asking them to locate the patients' GP records. The letter referred to the high mortality during the 1989-90 influenza epidemic and the concern voiced by the Chief Medical Officer and his Influenza Advisory Committee about the deaths and low levels of immunisation (Appendix IV). The letter also provided details of the proposed study; General Managers were informed that ethical approval had been obtained from the relevant DHAs and a copy of the ethical committee approval was also enclosed.

Each FHSA was visited when the GP records had been located and the records were reviewed. Using a proforma (Appendix V), information was collected on basic demography; the subjects' usual place of residence, classified into institutional (nursing and residential care homes, 'part III' accommodation, and long stay hospital beds, and non-institutional (all other residences including warden assisted complexes); the presence of chronic medical conditions until the beginning of the epidemic; the number of consultations with GPs during the 12 months before death; the number of hospital admissions during the 12 months and 5 years before death; influenza

vaccination during the five years before death; and details of the final illness including the date of onset and duration, the number of consultations with medical practitioners, admission to hospital, and the place of death. Fatal cases who received the 1989 - 90 vaccine up to December 15, 1989, and whose death was not less than two weeks after vaccination, were considered vaccinees for 1989. Fatal cases who received vaccine during one or more seasons between 1985 - 1986 to 1988 - 1989 were considered to be 'previous vaccinees'.

Identification of controls

Four controls for each fatal case matched for age (same year of birth), sex, and area of residence (same DHA), who survived the 1989 - 90 epidemic but died during week 44, 1990 (3.11.90 inclusive) to week 8, 1991 (22.02.91 inclusive) were randomly identified by the Office of Population Censuses and Surveys (OPCS). Photocopies of their death certificates were obtained from OPCS.

A letter was sent to mangers of FHSAs together with photocopies of death certificates of controls and they were asked to locate GP records. Each FHSA was visited and GP records were reviewed for the same information as obtained for cases using the proforma in Appendix VI. Controls who lived in a different DHA to cases during the epidemic were excluded. Controls who received the 1989 - 90 vaccine up to December 15, 1989 were considered vaccinees for 1989. Controls who received vaccine during one or more seasons between 1985-1986 to 1988-1989 were considered to be 'previous vaccinees'.

Classification of chronic medical conditions

Chronic medical conditions were identified from specific entries in GP records and hospital correspondence. An entry labelling a patient as suffering from a chronic medical condition was taken as evidence of the

presence of that medical condition irrespective of whether the patient was prescribed medications. Chronic medical conditions were grouped as chronic obstructive pulmonary disease (COPD) including asthma; other pulmonary disease; heart disease (including angina, arrhythmia, myocardial infarction, heart failure, hypertension, valvular heart disease, and cardiomyopathy); diabetes mellitus and other endocrine disease; renal disease; malignancy; neurological disease (including dementia, Parkinson's disease, and cerebrovascular disease); musculoskeletal and connective tissue disease; immunosuppression including haemopoetic malignancy and those taking steroids and immunosupressive medications; and other conditions. Information was also collected on body systems for which medications were prescribed.

Statistical analysis

Descriptive analyses were performed using SPSS-PC to calculate distributions of all variables by case or control status (Norusis, 1988). Further analyses were undertaken using conditional logistic regression for matched case control studies (Breslow and Day, 1980). Relative risks were estimated by odds ratio, and confidence intervals are given at 95%. Modelling, using EGRET, began by firstly considering 'current' influenza vaccination status, and disease variables with frequency distributions among cases significantly different from controls ($p < 0.05$); high-risk medical conditions which feature in the current Department of Health (DoH) recommendations for influenza immunisation were also included in the model at this stage regardless of significance (Department of Health, 1992). Afterwards, all remaining (non-significant) disease variables were added in turn, but only those which significantly altered the model were retained (musculoskeletal and connective tissue disease). The model therefore contained variables representing residential status (institutional versus community living), cardiac disease

(including hypertension), chronic obstructive pulmonary disease (COPD) including asthma, other pulmonary disease, renal disease, diabetes, other endocrine disorders, immunosuppression, neurological disease, musculoskeletal and connective tissue disease, malignancy, and 'current' influenza vaccination in the 1989 - 90 season. An adjusted odds ratio was calculated to show the risk of influenza death associated with each factor. In the next stage of analysis 'previous' influenza vaccination (defined as one or more instances of vaccination between 1985 - 86 and 1988 - 89) was added to the model; the interaction between 'previous' and 'current' vaccination in 1989 was then considered by addition of product terms. Finally, the model was developed to consider the effectiveness of vaccine in patients living in institutions compared to those living in the community; also among subjects with high-risk medical conditions, as specified by the DoH, compared to those without. Vaccine effectiveness (V_E) was determined using the formula: V_E = 1 - (odds ratio in vaccinated subjects) (Smith *et al.*, 1984).

For vaccine uptake multiple logistic regression was used to estimate the likelihood of influenza vaccination in 1989 - 90 by calculating the adjusted odds ratios with respect to potentially important explanatory variables. Confidence interval was given at 95%. The modelling strategy used was initially to fit a saturated model including age, sex, residential status (institutional versus community living), number of body systems affected by chronic diseases, number of body systems for which long term medications were prescribed, number of hospital admissions during the 12 months before death, number of hospital admissions during the five years before deaths, and 'previous' influenza immunisation between 1985 - 1988. Variables with no significant contribution to the model ($p > 0.05$) were removed one at a time until only those remaining in the model contribute significantly. The model therefore contained variables including number of GP consultations in the 12

months before death, residential status (institutional versus community living), and 'previous' influenza vaccination between 1985 - 1988.

7.3 Hospital admission study

The study was carried out between November 1993 and November 1994 in Leicestershire Health Authority with a resident population of 892,000 in 1989-90. Ethical approval was obtained from the Leicestershire Committee on the Ethics of Clinical Research Investigation.

Study power

Based on 156 cases, the study had a power in excess of 80% to detect an odds ratio of 0.4 (60% vaccine effectiveness) at 95% significance level.

Identification of cases

Cases were identified using Leicestershire Health Authority's Patient Administration System. All patients aged 16 years or over who were admitted to Leicestershire hospitals (15 in total) between December 1, 1989, and January 31, 1990 inclusive, and whose primary discharge diagnosis or cause of death was either influenza, pneumonia, emphysema, or bronchitis (*ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492) were identified as cases. Medical Records' Departments in the 15 hospitals located patients' notes.

The hospital records of cases were reviewed, and information was collected, using the proforma in Appendix VII, on basic demography; the subjects' usual place of residence classified into institutional (nursing and residential care homes, 'part III' accommodation, and long stay hospital beds), and non-institutional (all other residences including warden assisted complexes); the presence of chronic medical conditions until the beginning of the epidemic; number of hospital admissions during the last 5 years;

medications prescribed during the admission including dose, frequency and duration; length of hospital stay; and outcome.

Influenza vaccination history during the five years before admission in 1989 - 90 was obtained from general practitioners' records. General practitioners' records of deceased cases were located by Leicestershire Family Health Services Authority. A letter and proforma were sent to the general practitioner requesting vaccination history of surviving cases. The letter explained the background leading to the proposed research, the aims and objectives of the project, and methods to be employed. The proforma asked about vaccination history during the five years before admission; for each year the general practitioner was asked to state whether the patient received vaccine and, if yes, to provide the date of administration (Appendix IIX). A second request was sent to general practitioners who did not reply within two months. Cases who received the 1989 - 90 vaccine until December 15, 1989 and whose admissions were not less than two weeks after vaccination were considered as 'current' vaccinees. Admissions who received vaccine on one or more seasons between 1985 - 1986 to 1988 - 89 were considered as 'previous' vaccinees.

Identification of controls

Two controls matched for age (same year of birth) and sex but from a different general practice were identified for each case. For cases who died during the admission or up to nine calendar months after discharge, two controls who survived the 1989 - 90 epidemic but died more than 6 and less than 12 months after the index case were identified, being the first and second records matching the index case for age and sex in general practitioner records of deceased individuals retained by Leicestershire Family Health Services Authority.

Controls for survivors were selected from nine neighbouring general practices in Leicestershire using the same method. Neighbouring general practices were contacted by telephone and the study was explained to them. Subsequently details of the sex and year of birth of cases were sent to the neighbouring practice and practitioners were asked to select two controls for each patient. General practitioners' records of controls were reviewed, using the proforma in Appendix IX, for information on residential status classified into institutional (nursing and residential care homes, 'part III' accommodation, and long stay hospital beds), and non-institutional (all other residences including warden assisted complexes); presence of chronic medical conditions; and vaccination history during the 5 years before the 1989 - 90 epidemic. Controls who received the 1989 - 1990 vaccine up to December 15, 1989 were considered as 'current' vaccinees. Controls who received vaccine on one or more seasons between 1985 - 1986 to 1988 - 1989 were considered as 'previous' vaccinees.

Classification of chronic medical conditions

Chronic medical conditions were identified from specific entries in hospital and GP records. An entry labelling a patient as suffering from a chronic medical condition was taken as evidence of the presence of that medical condition irrespective of whether the patient was prescribed medication. Chronic medical conditions were grouped as chronic pulmonary disease including asthma; heart disease (including angina, arrhythmia, myocardial infarction, heart failure, hypertension, valvular heart disease, and cardiomyopathy); diabetes mellitus and other endocrine disease; renal disease; malignancy; neurological disease (including dementia, Parkinson's disease, and cerebrovascular disease); musculoskeletal and connective tissue disease; immunosuppression including haemopoetic malignancy and those taking steroids and immunosupressive medications; other conditions.

Information was also obtained on body systems for which medications were prescribed.

Statistical analysis

Descriptive analyses were performed to describe the distribution of each variable (including 'current' and 'previous' vaccination) by case or control status. Subsequently conditional logistic regression methods for matched case control studies were employed. A model was constructed containing firstly those variables with frequency distributions which differed significantly ($p < 0.05$) between cases and controls (chronic pulmonary disease, musculoskeletal/connective tissue disease, and institutional living); variables representing the remaining high-risk medical categories specified by the DoH (Department of Health, 1992) were also included as were neurological disease, malignancy and 'previous' influenza vaccination because the mortality study had shown these to be determinants of death from influenza. 'Current' influenza vaccination was then added to the model, and percent vaccine effectiveness was calculated as 1 minus the odds ratio in vaccinated subjects (Smith *et al.*, 1984). In extensions to the basic model, product terms were added to explore the possibility that vaccine effectiveness was different among patients living in institutions compared to those in the community, and between patients with high-risk medical conditions (Department of Health, 1992) and those without.

Calculation of costs of hospital admissions

A random sample of 50 patients were selected from all 264 admissions for whom hospital case notes were available using the Minitab software package release 8.2 on an Apple Macintosh LC computer. For each of the 50 patients the number and type of all laboratory tests, radiological, and other investigations carried out during admission were obtained from hospital

records. Costs of Laboratory tests, radiological, and other investigations were obtained from relevant departments at Leicester Royal Infirmary. Also the types of drugs used, route of administration, and duration of in-patient treatment were collected from hospital records. Drug costs were obtained from British National Formulary, 1996 (British Medical Association and Royal Pharmaceutical Society of Great Britain, 1996).

RESULTS

Mortality Study

CHAPTER 8

Delays and diversity in the practice of local research ethics committees

8.1 Introduction

Local research ethics committees (LRECs) in Britain developed following Royal College of Physicians (RCP) recommendations in 1967 which were subsequently disseminated by the Ministry of Health (Royal College of Physicians, 1967; Ministry of Health, 1968). Further guidance was provided by the RCP in 1973 which was endorsed by the Department of Health in 1975 (Department of Health and Social Security, 1975). The RCP has updated its guidance (Royal College of Physicians, 1984, 1986, 1990), and additional discussions and guidance on ethical issues relevant to medical research have been published in Britain (Working Party on Ethics of Research in Children, 1980; Department of Health and Social Security, 1984; Harding, 1986). Nonetheless surveys of LRECs suggest that the guidelines have had little impact on the composition and practice of the LRECs (Gilbert, 1989; Neuberger, 1992). Multi-centre studies have become increasingly more common with a recent survey revealing that they represent 18% of the workload of LRECs (Moran, 1992).

Because of the ever increasing necessity for national and international multi-centre studies, it is essential that patients' interests are safeguarded and ethical approval obtained in the most efficient way. The following provides an analysis of the difficulties and delays encountered in obtaining ethical approval for the mortality study.

8.2 Results

Response of the chairmen of LRECs

A total of 36 chairmen of LRECs were contacted and replies were received from all 36. Four (11%) granted chairman's approval, but two of the four required completion of their LREC application form. One of the four required additional information, and chairman's approval was subsequently granted. The remaining 32 chairmen (89%) required our proposal to be considered by their LREC, and 19 (59%) wanted us to complete their local application forms, a copy of which was sent with the reply. Altogether 21 committees required completion of their local application forms. Of the 32, three committees requested that one of the investigators attend their meeting to discuss the proposal.

Questions asked in LRECs application forms

Analysis of 20 of the 21 LREC application forms (one application form was for questionnaire based research, and was not included in the analysis) revealed considerable variation in the number and type of questions asked. None conformed exactly to the suggested format for applications to research ethics committees as proposed by the RCP (Royal College of Physicians, 1990) (Table 8.1). Only 2 (10%) LRECs included questions relating to paediatric research, and only 2 (10%) referred to specially vulnerable groups. Three committees (15%) required a statement on the personal experience of the applicant in the field of investigation concerned.

Time taken (days) to obtain ethical approval

The interval between sending applications to 36 LRECs and receiving approval ranged from 6 to 208 days (median 61 days). The interval between sending the application and obtaining chairman's approval averaged 35 days (range 6 to 70 days) and for obtaining full committee approval averaged 77

days (range 18 to 208 days). Figure 8.1 shows that one third of the LRECs were unable to approve the project within three months, and three of the 36 LRECs took longer than six months.

Questions	No. of LRECs (percentage)
State the title of the proposed project.	20(100)
State the question to be answered and the value of answering it.	20(100)
Give an outline of the proposed project including procedure, measurements, data analysis.	19(95)
State the manner in which the subjects' consent will be obtained.	19(95)
Specify the type of subjects, how they will be recruited.	18(90)
State the potential hazards to subjects, and their estimated probability and the precaution to be taken to meet them.	18(90)
State the procedures which may cause discomfort or distress.	18(90)
If the project is designed to test a *drug or appliance*, state its exact regulatory status.	16(80)
Attach any other relevant matter.	15(75)
Is the study sponsored by an industrial company?	15(75)
What arrangements, if any, for compensation in the event of injury to subjects have been made?	14(70)
State any payments to subjects.	14(70)
State the likely duration of the project and the premises in which it will be undertaken.	12(60)
State any profit, personal or departmental, financial or otherwise, relating to the study.	12(60)
State whether subjects' general practitioner is to be informed of recruitment of the subjects.	11(55)
Specify whether subjects are in a dependent relationship with investigator.	6(30)
State the personal experience of applicant in the field of investigation concerned.	3(15)
Specify whether subjects are specially vulnerable, eg children, mentally handicapped.	2(10)
Has the company provided a written statement that it accepts the current Guidelines of the Association of the British Pharmaceutical Industry?	2(10)
For paediatric projects: In what way can the proposed investigation be expected to benefit the individual patient, or a near relative.	2(10)
If the investigation can not be expected to benefit the individual patient: (a) are the risks minimal?	2(10)
(b) Is parental or guardian agreement to be obtained?	2(10)
(c) Is the child capable of giving assent?	2(10)

Table 8.1: **Issues raised on ethical committee forms with reference to RCP guidelines.**

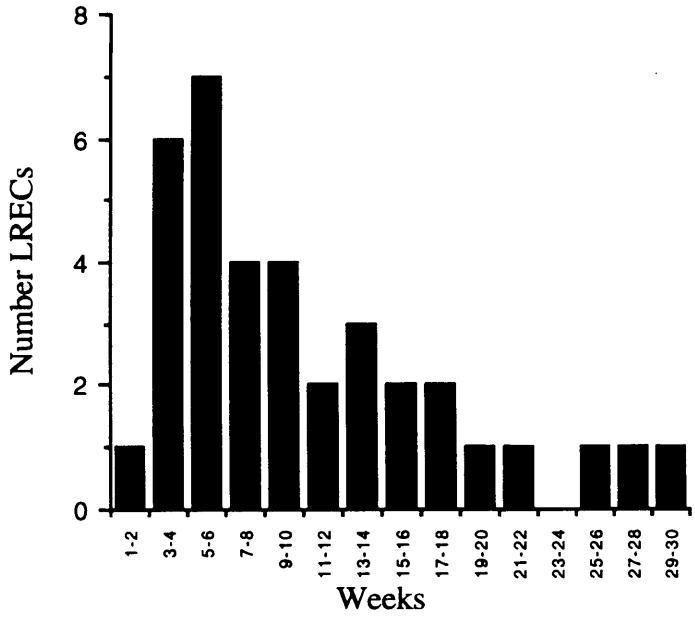

Figure 8.1: **Interval between the sending of applications to 36 research ethics committees and approval.**

8.3 Discussion

The LRECs involved in this study may not have been a randomly selected sample, nevertheless they extend over a wide geographical area covering six Health Regions in England, and hence reasonable conclusions can be drawn from this experience.

The response to our research proposal was diverse, ranging from no further ethical approval required, chairman's approval after completion of local research ethics committee application form, chairman's approval after provision of additional information, consideration of the submission by the full committee, consideration of a completed local research ethics committee form, and actual attendance at the ethics committee meeting. There is room for some diversity among ethics committees because of the subjective nature of ethical considerations and local needs. Admittedly in some of the areas in which we encountered different practices there are no clear guidelines. For example, there are no strict rules on the frequency of LREC meetings or whether they should be attended by the investigators. However, in areas where guidelines exist, the analysis highlighted a great degree of variation in the information asked of researchers. The RCP guidelines were issued in 1990 yet by the end of 1992 none of the 20 LREC application forms conformed exactly to the guidelines. Failure to follow issued guidelines has been discussed before (Thompson *et al.*, 1981; Gilbert *et al.*, 1989), and improving communication, by adopting a registration system for LRECs, and training potential committee members have been suggested as solutions (Gilbert *et al.*, 1989), but have not been implemented.

Obtaining ethical approval for multi-centre studies is time consuming in the absence of a central review body. Evidently most LREC chairmen do not grant approval for studies approved elsewhere, and require a full submission to be made for local consideration. Overall one third of the LRECs were unable to approve the project within three months, and 3 of the

36 (8%) took longer than six months. As none of the committees rejected our submission, or required modification, delays in obtaining approval evidently relate to the frequency with which ethics committees meet and their work load. The process of identifying and locating chairmen of ethics committees, and obtaining and completing application forms was also time-consuming and therefore expensive. The average cost, including photocopying, postage, telephone calls, travel and time of research worker was estimated at approximately £25.5 per district, amounting to more than £900 for the study. Had the study required approval throughout England and Wales the cost of obtaining ethical approval is estimated in excess of £5000.

A central system for obtaining ethical approval for multi-centre studies was suggested in recent Department of Health guidelines (Department of Health, 1991). However, the Department of Health guidelines also recommended that the right of individual committees to call for review of proposal should be retained. Horwitz, (1994) suggested a system based on establishing a co-operative database of all LRECs in England. Researchers seeking ethical approval for a multi-centre study would submit the protocol to any two LRECs in the collaborating group. The two LRECs involved would be informed of the other's involvement and would be able to discuss difficulties between them. Once approval was granted researchers circulate the letter of approval together with a copy of protocol to the other collaborating LRECs. However, LRECs would have the power of veto.

Historically LRECs developed according to their own views. In the early stages of their development no specific guidelines on practices and methods were given because it was thought that strict rules of conduct would not be adaptable to local needs. LRECs have undoubtedly played a significant role in safeguarding patients' interests and deal with a significant work load, amounting in some instances to reviewing 400 submissions a year (Royal College of Physicians, 1990). The two cardinal assets of LRECs are

their independence and invaluable local knowledge and because of the latter there are, arguably, advantages to decisions made locally. Suggestions have, however, been made to try to preserve the independence of the LRECs on one hand and to avoid undue delay and unnecessary administrative work on the other (Moran, 1992). Consensus has yet to be reached. There is no evidence that repetitive review by many LRECs will provide greater protection for patients (Hotopf, 1995). Difficulties encountered as a result of repetitive review were recently highlighted in a report where 5 of 6 committees demanded changes to the proposal; none of them asked for the same changes (Horwitz, 1994)

A system based on adoption of a standard application form for researchers seeking approval for multi-centre studies, and setting a central or regional committee to give conditional approval and send a copy of the protocol or a summary with the letter of approval to all LRECs involved constitutes a workable solution in the present system. By sending a copy of the full protocol or a summary, LRECs should have sufficient understanding of the scientific basis of the research project and its aims. Such a system should reduce bureaucracy by substantially reducing the amount of paperwork and expense involved in making multiple submissions. Moreover, it would reduce the burden on LRECs whose members usually have many other commitments and are unpaid. The role of such a committee should focus on the ethics of research, yet embrace scientific and statistical considerations, and its duties should be extended to include both clinical and epidemiological projects. The decisions of a central or regional committee should be binding on LRECs, however their right to modify consent forms and patient information may be retained, since these are areas where their invaluable local knowledge is advantageous. It would be important for such a committee to be independent and therefore its funding should be arranged centrally. Its membership could include lay people and senior and

experienced people of distinction in their field who may be nominated by: the General Medical Council, DoH, RCP, Royal College of Nursing, Medical Research Council, The Association of Medical Research Charities, and The Association of British Pharmaceutical Industry.

My limited experience reveals that there is much diversity in the practice of LRECs. The data presented clearly support the need for a central or regional review process for multi-centre studies, but it is essential that the review process addresses the perceived needs of all ethical committees in the United Kingdom and that it is periodically audited.

CHAPTER 9

Vaccine effectiveness in reducing mortality and risk factors for fatal influenza

9.1 Introduction

Influenza vaccine uptake in the UK is unacceptably low. Less than 50% of those at risk are immunised each year (Nguyen-Van-Tam and Nicholson, 1993), with scepticism about vaccine effectiveness being partly responsible for the low uptake. Lennox *et al.*, (1990) in a survey of 477 consultant geriatricians in the UK., showed that 385 (81%) had never offered influenza vaccine to patients in continuing-care wards. Of the 385, 128 consultants (33%) regarded the vaccine as ineffective.

Sceptisism about the effectiveness of repeated influenza vaccination may also contribute to poor immunisation levels. Much emphasis has evidently been placed on the study by Hoskins *et al.*, (1979). These investigators assessed the protective effect of inactivated influenza vaccine against influenza after three outbreaks of influenza at a boys' school. They suggested that annual revaccination with inactivated influenza A vaccine conferred no long term advantage. In another study, inactivated vaccine produced about 80% protection against influenza in a group of hospital staff who had received few if any annual vaccinations, whereas the incidence of influenza in elderly institutionalised individuals, who were said to be regular vaccinees, was not reduced (Feery *et al.*, 1979). However, this latter group benefited from a moderation in the severity of the clinical picture in comparison with non-vaccinees. More recent data suggest that repeated annual immunisation may actually improve protection against illness (Keitel *et al.*, 1988). Therefore the value of repeated immunisation remained controversial when this work was undertaken and Keitel *et al.*, did not considered mortality or other severe sequelae as an outcome.

Although influenza vaccine offers 60 to 80% protection against influenza-like illness in the young and healthy (Gundelfinger, 1958), the protection afforded in the elderly is less - about 20% (Patriarca *et al.*, 1986). Of greater relevance, however, are reductions in the incidence of bronchopneumonia (49-90%; mean 69%), hospitalisations (47-72%; mean 59%), and deaths (0-100%; mean 69%) that may occur in elderly subjects when vaccine and epidemic strains are similar (Nicholson, 1992). However the majority of these studies involved elderly patients in residential care with no distinction between those with and without chronic diseases. They were also uncontrolled and the possibility that vaccine was withheld from patients with poor quality of life and/or that medical management of non-vaccinees was different to vaccinees can not be ruled out. Therefore, there is uncertainty about the value of vaccine in the fit elderly, non-residential elderly with chronic disease, and the elderly in residential care.

The unpredictability of influenza epidemics, and ethical considerations effectively prevent placebo-controlled studies of licensed vaccines in high risk subjects. Case-control studies provide an alternative method of assessing vaccine effectiveness (Comstock, 1990). The A/England/308/89 (H3N2) epidemic, which occurred during the winter of 1989/90, provided the opportunity to study vaccine effectiveness in reducing mortality during a period when vaccine and wild strains were well matched. The findings are reported below.

9.2 Results

A total of 412 fatal influenza cases were identified. Figure 9.1 shows the chronology of the deaths and consultation rates for influenza as reported by the Royal College of General Practitioners (RCGP) "spotter practices" for the 412 cases. Of the 412 cases, GP records were available for 315, for whom 1256 controls were initially matched; however GP records were only available

for 777 controls. Controls could not be obtained for seven cases, reducing the number of matched sets used in the regression analysis from 315 to 308. Table 9.1 shows the primary and contributary causes of death in control subjects. None of the controls were certified as dying from influenza; 221 (28.4%) had pneumonia recorded as a primary cause of death. The characteristics of cases and controls with respect to age, chronic disease, residential status, pneumococcal and influenza vaccination are shown in Table 9.2. Amongst cases, 18.1% had received vaccine in 1989/1990 compared to 22.9% of controls, yielding an odds ratio of certified influenza death in vaccinated subjects of 0.74 (95% CI 0.53% - 1.05%), giving an estimated vaccine effectiveness of 26% (95% CI 0% - 47%).

The independent effects of each variable on the likelihood of certified influenza death are shown in Table 9.3 as odds ratios. Subjects with COPD and asthma, neurological disease, and those in institutions were at significantly increased risk of influenza death. Overall the risk of certified influenza death in the DoH designated high-risk group was increased by about 60%. The exclusion of subjects with lone hypertension when adjusting for the effect of cardiac disease produced odds ratios that were virtually identical.

Having adjusted the logistic equation for the effect of underlying chronic disease, the odds ratio for certified influenza death in vaccinated subjects fell to 0.59 (95% CI 0.40 - 0.87) giving an estimated vaccine effectiveness of 41% (95% CI 13% - 60%). When additional adjustments were then made for the effect of previous vaccination, and its interaction with current vaccination, both were found to alter the model significantly ($p= 0.03$ and 0.02 respectively). Vaccine effectiveness was estimated to be 9% (95% CI 0% - 59%) among first time vaccinees, rising to 75% (95% CI 31% - 91%) among subjects who had also been vaccinated previously; however on its own previous vaccination conferred no benefit

in protecting against influenza death in the 'current' season (Table 9.4). After those adjustments had been made no further significant interactions were found between the effect of vaccine in institutions and the open community ($p = 0.16$), and between subjects with high risk medical conditions as specified by the DoH and those without ($p = 0.76$).

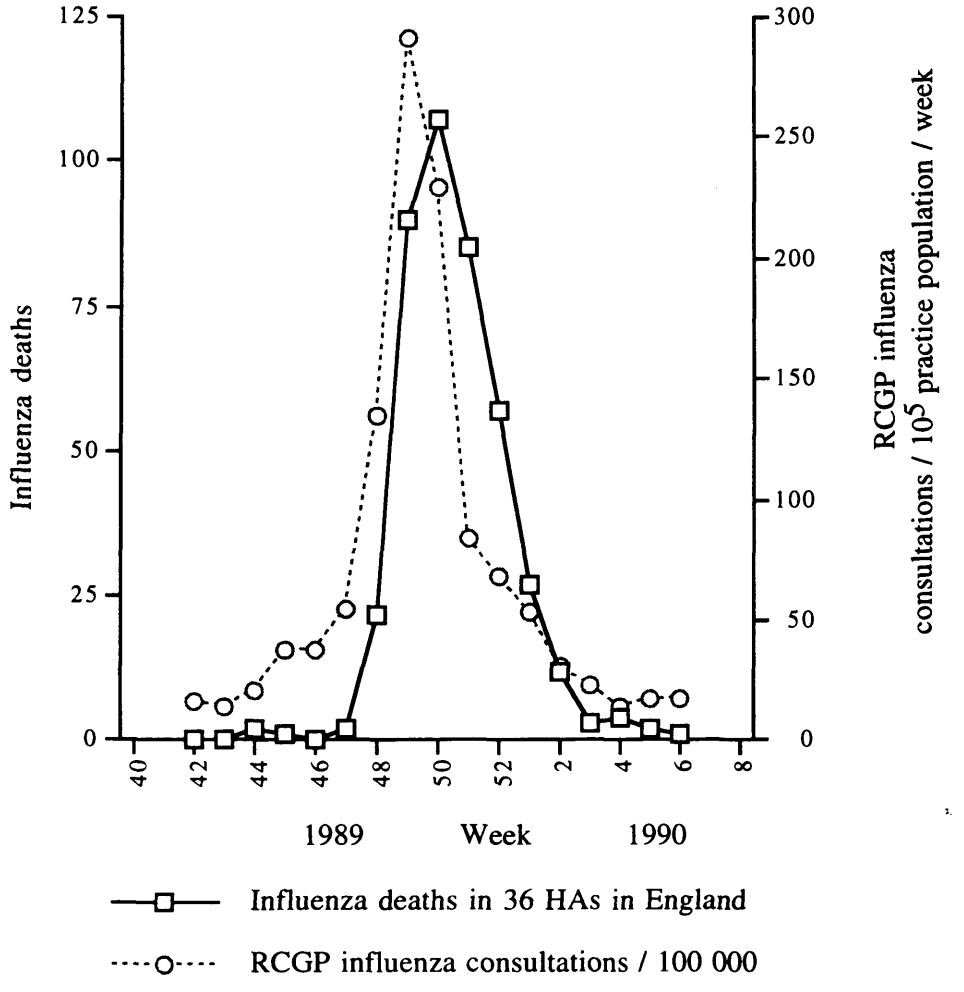

Figure 9.1: **Temporal relation between certified influenza deaths in 36 DHAs and 'influenza' consultation rates in sentinel practices.**

Cause of death	Ia	Ib	Ic	II
Pneumonia	221	6	1	10
Cardiovascular disease	275	231	61	66
Other pulmonary disease	22	31	5	18
Neurological disease	76	52	10	67
Diabetes mellitus	0	9	4	23
Renal disease	15	5	0	8
Malignancy	139	108	12	21
Old age	7	8	3	8
Infection (other than pneumonia)	5	7	1	4
Musculoskeletal and connective tissue disease	0	0	0	10
Other causes	15	30	16	32
No cause mentioned	0	289	663	509
Data not legible	2	1	1	1

Table 9.1: **Cause of death for the 777 controls.**

Ia = Directly leading to cause of death.

Ib = Directly leading to 1a.

Ic = Directly leading to 1b.

II = Other conditions contributing to the death, but not related to the disease causing it.

Characteristic	Number (percentage)	
	Cases (n=315)	Controls (n=777)
Age in years		
16 - 44	1 (0.3)	0 (0.0)
45 - 64	15 (4.8)	30 (3.9)
65 - 74	38 (12.1)	104 (13.4)
75 - 84	107 (34.0)	241 (31.0)
85 - 94	135 (42.9)	372 (47.9)
≥ 95	19 (6.0)	30 (3.9)
Mean age (SD) in years	82.6 (9.1)	83.1 (8.4)
Median age in years	84	85
Sex:		
Male	101 (32.1)	246 (31.7)
Female	214 (67.9)	531 (68.3)
Residential status		
Institution*	162 (51.4)	262 (33.6)
Community	153 (48.6)	515 (69.3)
Chronic diseases:		
Heart disease*	130 (41.3)	373 (48.0)
COPD and asthma*	65 (20.6)	108 (13.9)
Other pulmonary disease*	6 (1.9)	9 (1.2)
Renal disease*	6 (1.9)	13 (1.7)
Diabetes*	24 (7.6)	73 (9.4)
Other endocrine disease*	22 (7.0)	27 (3.5)
Immunosuppression*	1 (0.3)	11 (1.4)
Malignancy	15 (4.8)	106 (13.6)
Neurological disease	122 (38.7)	180 (23.2)
Musculoskeletal and connective tissue disease	41 (13.0)	144 (18.5)
Influenza vaccine recommended by DoH		
Yes	263 (83.5)	577 (74.3)
No	52 (16.5)	200 (25.7)
Influenza vaccine received		
1989 only	25 (7.9)	42 (5.4)
1985 - 1988 only	12 (3.8)	23 (3.0)
Both	32 (10.2)	136 (17.5)
Neither	246 (78.1)	576 (74.1)
Pneumococcal vaccine in the last 5 years		
No	81 (25.7)	394 (50.7)
Data not collected	234 (74.3)	383 (49.3)

* DoH designated high-risk group.

Table 9.2: **Demographic characteristics, chronic ill-health and residential status of cases and controls.**

Factor	Odds ratio of certified influenza death (and 95% confidence interval
Institutional care*	2.08 (1.48 - 2.90)
COPD and asthma*	1.95 (1.33 - 2.87)
Neurological disease	1.65 (1.19 - 2.28)
Other endocrine disorders*	1.57 (0.83 - 2.95)
Renal disease*	1.43 (0.44 - 4.61)
Other pulmonary disease*	1.16 (0.34 - 3.88)
Cardiac disease*	0.71 (0.52 - 0.97)
Immunosuppression*	0.71 (0.08 - 6.15)
Diabetes mellitus*	0.66 (0.38 - 1.15)
Musculoskeletal and connective tissue disease	0.59 (0.38 - 0.91)
Malignancy	0.37 (0.20 - 0.67)
DoH designated high risk category	1.61 (1.11 - 2.33)

*DoH designated high-risk groups

Table 9.3: **Risk factors for certified influenza death during the 1989/90 influenza A epidemic.**

	Odds ratio for certified influenza death	Significance of likelihood ratio	Percentage vaccine efficacy (and 95% confidence interval)
Previous vaccination only (between 1985 - 1988)	1.2	0.66	0 (0 - 47)
First-time vaccination in 1989	0.91	0.83	9 (0 - 59)
Vaccination in 1989 and previously (between 1985 - 1988)	0.25	0.008	75 (31 - 91)

Table 9.4: **Effectiveness of influenza vaccine in 1989/90 according to current and previous vaccination status.**

9.3 Discussion

Study design

It has been argued that influenza epidemics kill people who would have died anyway during the next few months due to underlying illness. Ashley *et al.*, (1991) compared the daily number of deaths following the 1989/90 epidemic with the daily average number of deaths during the corresponding periods in 1985/86 to 1988/9. They found that from mid-January, 1990, daily deaths were lower than expected for a period of three months. Eickhoff *et al.*, (1961) noted similar deficit of deaths, from June through August, 1958, following the 1957/58 epidemic. They concluded that the deficit represented a "compensatory" phenomenon – a result of the premature death, due to epidemic influenza, of individuals who would have died within six to 12 months from their primary disease alone. We chose a control group who were generally so debilitated that they died 12 months after the 1989 - 90 epidemic. We reasoned that their survival during the epidemic may have been due to a protective effect of vaccination and tested this hypothesis. Ashley *et al.*, (1991) found that there was great variation in 'intensity' of the 1989/90 epidemic, as reflected by variation in mortality rates, in different regions in England. Accordingly, the controls were matched by geographic location and would be expected to have been exposed to the same influenza strains and intensity of activity as cases. Controls were not matched by medical practitioner in order to avoid overmatching caused by practice-wide policies for influenza vaccine.

Chronic heart disease, and diabetes mellitus were shown in several studies to be risk factors for fatal influenza (Barker and Mullooly, 1982; Bouter *et al.*, 1991; Moss *et al.*, 1991). The study did not confirm these risk factors individually possibly because they were important factors contributing to the death of controls or because of small numbers. Nevertheless the validity of the study design was supported by the finding

that the risk of influenza death among groups for whom the Department of Health strongly recommends vaccination was more than doubled (Department of Health, 1992).

The study focused on 315 certified deaths that were attributed partly or wholly to influenza by clinicians, without laboratory confirmation. Certified influenza deaths closely match influenza epidemic curves for virus reports, GP consultations for influenza and influenza-like illness, and excess deaths (Nguyen-Van-Tam and Nicholson, 1992). This approach sacrifices specificity of the diagnosis but nevertheless considers cases that contributed to the excess mortality. Ideally the study should have focused on cases where influenza was confirmed by laboratory tests, but medical practitioners in Britain seldom obtain nasopharyngeal specimens during acute respiratory episodes, and diagnostic influenza serology was precluded by deaths. The 1989/90 epidemic resulted in the highest laboratory reporting of influenza since 1975/76 and during such outbreaks the clinical diagnostic rate as later assessed by serology averages about 80% (Little *et al.*, 1978; Van Voris *et al.*, 1981; Hall *et al.*, 1987). Of the 315 fatal cases, 273 (87%) had been seen by a general practitioner on at least one occasion during their final illness (figure 11.1), over half lived in residential care, and 54 (17%) were hospitalised during their final illness (table 11.1), so death certification was supported by clinical observations over several days for most patients and the diagnostic rate is therefore likely to have been high.

It is unlikely that significant bias was introduced through influenza death certifications being made more frequently for non vaccinees as compared with vaccinees for the same clinical problem. The certifying doctor would probably not have known the patient's vaccination status at the time of certification without reference to GP records, and vaccine may well have been administered by the practice nurse. Undoubtedly some deaths, even those occurring at the epidemic peak, were due to conditions

other than influenza. This would result in a misclassification bias and diminish the estimates of vaccine effectiveness, so the overall estimates for the effectiveness of influenza vaccine in reducing deaths are considered conservative. However, the effectiveness will be less during years when there are mis-matches between vaccine and wild-type strains.

In Britain influenza vaccine is available only by prescription, and the administration of any injection is of potential medico-legal importance. Therefore, the possibility of systematic under-reporting of instances of immunisation in GP records is remote, and no more likely to occur in cases than controls. Furthermore, the vaccination rates of 18.1% among cases and 22.9% among controls are similar to the uptake described in other studies in England that took place around the 1989/90 epidemic (Nicholson, 1987; Kurinczuk and Nicholson, 1989; Wiselka *et al.*, 1992).

Vaccine effectiveness in reducing mortality

This study has shown that influenza vaccine reduced influenza mortality by 41%. This estimate is in agreement with observational studies: Arden *et al.*, (1986) reviewed two studies in nursing home residents and found that influenza vaccine reduced mortality by a mean of 67%. Gross *et al.*, (1995) conducted a meta-analysis of 20 cohort studies and found that the pooled estimates of vaccine effectiveness in preventing deaths was 68% (CI 56% - 76%). Similar results were found in two recently published North American case-control and cohort studies which considered pneumonia and influenza mortality among admissions, and deaths from all causes as outcomes. Fedson *et al.*, (1993) compared the prevalence of chronic medical conditions and influenza immunisation status in over 5000 non-institutionalised subjects admitted to Manitoba hospitals for lower respiratory tract conditions during two seasons of influenza A (H3N2) activity, with controls matched for age, sex and place of residence. Influenza

vaccine was 43 - 65% effective in preventing hospital deaths from respiratory conditions and 27 - 30% effective in preventing deaths from all causes. Nichol *et al.*, (1994), in cohort study, studied vaccine effectiveness over three seasons 1990 to 1993. Each cohort included more than 25,000 non-institutionalised individuals aged 65 years or over. Vaccination was 39 - 54% effective in preventing death from all causes. Our findings also accord with a recently published cohort study using computerised general practitioners' records on about 10,000 patients aged 55 years or older (Fleming *et al.*, 1995). These investigators found that recent influenza immunisation afforded a 75% (95% CI 21 - 92%) protection against death from all causes. In addition, our study has shown that repeated annual vaccination appears to confer a greater reduction in mortality (75%) than after first time immunisation. For those who received the vaccine for the first time in 1989 vaccine effectiveness was 9% (CI 0 - 59%). However, the 95% confidence interval for this estimate was wide possibly due to the relatively small number of first time vaccinees (67 individuals received vaccine in 1989 for the first time, and 168 received vaccine in 1989 and previously).

Although little used in Britain, the role of pneumococcal vaccine in preventing 'influenza' death was assessed in 81 (25.7%) cases and 394 (50.7%) controls. The indications for its use are similar to those for influenza vaccine yet none of the 475 cases and controls had received pneumococcal vaccine in the preceding five years. It is therefore highly unlikely that the beneficial effect of influenza vaccine was in reality due to pneumococcal vaccine.

Risk factors for fatal influenza

The study has shown that residential care, COPD and asthma are independent risk factors for fatal influenza. This is in agreement with

previous studies adopting data from mortality statistics (Eickhoff, 1961), and more recent studies quantifying the risk of dying from influenza with respect to presence of chronic medical conditions and residence in institutions (Barker and Mullooly, 1982; Nguyen-Van-Tam and Nicholson, 1992). The study also found neurological disease to be an independent risk factor for fatal influenza. Neurological disease in this study included cerebrovascular, Parkinson's disease, and dementia. Although vascular disease has been shown to be a risk factor for fatal influenza in several studies (Eickhoff, 1961; Barker and Mullooly, 1982), Parkinson's disease and dementia are not recognised as such. However, a recent study from Michigan, USA, used data from death certificates and compared underlying causes of death for two populations: those over 40 years of age for whom Parkinson's disease was listed as a contributing cause of death in the years 1970 through 1989, and all persons over 40 years of age who died in 1970, 1980, or 1990. Parkinson's disease patients were found to be three to four times more likely to die from influenza and pneumonia (proportionate mortality ratio 3.55; 95% CI 3.5 to 3.6) (Gorell *et al.*, 1994). Persons with dementia are at an increased risk for serious pulmonary infections with organisms that have been associated with influenza, and about 70% of patients with dementia die of bronchopneumonia (Molsa *et al.*, 1986; Burns *et al.*, 1990). It is, therefore, not surprising to show that neurological disease is an independent risk factor for fatal influenza.

The study has shown that individuals with musculoskeletal and connective tissue disease were less likely to die from influenza. This finding is at variance with the observation reported by Ashley *et al.*, (1991) that musculoskeletal deaths increased by 30% during the 1989-90 influenza epidemic. However Ashley *et al.*, (1991) obtained their data from certified cause of death without reviewing patients' records. Several studies have shown that over reliance on certified cause of death can lead to serious

statistical inaccuracies in epidemiological research (Zumwalt and Ritter, 1987; McKelvie, 1993). Conceivably a protective effect of musculoskeletal disease from influenza death may occur through the use of non-steroidal anti-inflammatory medications. It has been shown that prostaglandin of the E series mediate immune inhibition (Rappaport and Dodge, 1982) and in one study acetylsalicylic acid, a prostaglandin inhibitor, was shown to significantly increase the proportion of subjects with a 4-fold rise in antibody against influenza A/Beijing following vaccination (Hsia, 1994).

A rather unexpected finding is that the presence of malignant disease seems to protect against death from influenza. The likely explanation for this finding is the spuriously higher prevalence of malignant disease among controls who all died one year after the epidemic, and whose deaths reflect the prevalence of medical conditions leading to death, rather than the prevalence of medical conditions in the general population. Cancer is predominantly a disease of old age and the rates of newly diagnosed malignant disease increase steadily with age. The rates of newly diagnosed cancer increase by about 23% at five year-intervals for those 65 years or older (OPCS, 1987). No similar increase is noted for other conditions such as cardiac or pulmonary disease for example.

Effectiveness of repeated annual vaccination

The question of whether repeated annual vaccination confers any benefit has been controversial for almost 20 years. In the absence of a new pandemic strain of influenza, trials such as the Christ's Hospital study are unlikely ever to be repeated (Hoskins *et al.*, 1979). A statistical re-appraisal of the Christ's Hospital study shows that analysis restricted to boys present in the school during outbreaks in 1972, 1974 and 1976 does not substantiate a lower attack rate in those vaccinated with A/ Port Chalmers vaccine for the first time compared to those vaccinated in 1974 and 1975, as suggested by the

authors (Hoskins *et al.*, 1979). Moreover Hoskins *et al* (1979) provided no data concerning the severity and duration of illness in those affected. These may be relevant since Feery *et al.*, (1979) found that even when repeated vaccination was ineffective in preventing infection it appeared to ameliorate illness, i.e., protect against more severe influenza. Keitel *et al.*, (1988) examined the effectiveness of sequential annual vaccination in a prospective placebo-controlled study in healthy 30 - 60 year old adults. In contrast to the boarding school study (Hoskins *et al.*, 1979) effectiveness was somewhat greater after repeated annual vaccination than after first time administration. Modest reductions in influenza infection related illness, reduction in moderate to severe lower respiratory and/or sytemic illness due to influenza and reduction in influenza virus shedding were significant in the repeat immunisation group only. More evidence for the effectiveness of repeat immunisation in preventing serological influenza has recently been produced by Govaert *et al.*, (1994). These investigators undertook a large randomised double-blind placebo-cotrolled study of influenza vaccine in elderly people and demonstrated higher levels of protection against serologically-confirmed influenza among those previously vaccinated. The findings of the present study accord closely with those of both Keitel *et al.*, (1988) and Govaert *et al.*, (1994).

Keitel *et al.*, (1988) used a whole virion vaccine whereas Govaert *et al.*, (1994) used a purified split virus vaccine. Both vaccine types contain viral components which may evoke important cell-mediated responses. It is conceivable that the greater protection of repeat immunisation in these studies is related to cell mediated immunity since haemagglutination inhibition titres to 'current' vaccine strains of those immunised 'currently' and 'previously' are lower than those vaccinated 'currently' but not 'previously' (Govaert, 1994). However, the role of cell mediated-immunity in influenza remains enigmatic since cytotoxic T

lymphocyte responses to vaccination are considered to be of relatively short duration (Powers and Belshe, 1993). Moreover cytotoxic T lymphocyte responses to vaccination do not vary in magnitude in persons with, versus those without, a history of prior influenza vaccination (Powers and Belshe, 1993).

Given the large size of the elderly population in Britain and that the number of those over 75 years is projected to increase by almost 10% during the next decade (OPCS Monitor PP2 89/2, 1989) an overall 41% reduction in certified influenza deaths and any concomitant reductions in medical consultations, drug costs and hospitalisations could represent a considerable reduction in health costs. The results presented in this study support the current British guidelines for annual vaccination, as well as the ongoing effort to increase vaccine coverage in at risk groups beyond present levels.

CHAPTER 10

Influenza vaccine uptake

10.1 Introduction

Recommendations for influenza vaccination are issued annually by the Department of Health (DoH), the Welsh Office, and the Scottish Home and Health Department. In spite of these recommendations, vaccine uptake in the UK remains unacceptably low at 10 to 40% (Lennox *et al.*, 1990; Nicholson *et al.*, 1987; Nguyen-Van-Tam and Nicholson, 1993). The 1989 - 90 influenza epidemic was the worst in the UK since 1976; it caused an estimated 29,000 deaths (Ashley *et al.*, 1991). The Chief Medical Officer (CMO) and his Influenza Advisory Committee were extremely concerned about the deaths and the low level of immunisation, and the CMO`s annual recommendations on influenza vaccine have since been strengthened (Department of Health, 1992). Although there has been an increase in the number of people vaccinated each year, large deficiencies in the delivery of vaccine to 'high-risk' groups still exist (Nicholson *et al.*, 1987; Nguyen-Van-Tam and Nicholson, 1993). The reasons for the low immunisation rate are unclear. A survey of general practices conducted in England in 1992 revealed that 89% had an agreed policy for influenza immunisation (Nguyen-Van-Tam and Nicholson, 1993). However, a questionnaire survey carried out in Leicestershire in 1991/92 revealed vaccine uptake of about 40% among patients with heart disease, lung disease, or diabetes mellitus which was at variance with stated policies (Nguyen-Van-Tam and Nicholson, 1993).

A more detailed analysis of differences between vaccinees and non-vacinees may cast more light on the reasons for the low immunisation rate and suggest ways by which vaccine uptake can be increased. The

following analyses concern subjects in a wide geographic area covering five health regions in England.

10.2 Results

General practitioners' records were reviewed for 315 cases and 777 controls (total 1092). Table 10.1 shows influenza vaccine uptake between 1985 - 86 and 1989 - 90 among cases and controls. Table 10.2 shows the demographic characteristics, health status categorised as high-risk groups for whom influenza vaccination is recommended by the DoH, hospital admissions, and vaccination status of all 1092 subjects. Two hundred and thirty five (21.5%) individuals received vaccine in 1989-90. More than three quarters of all patients had one or more conditions classified as risk factors for influenza complications and death by the Department of Health. Almost 40% had been admitted to hospital during the last five years.

Of the 840 individuals who had one or more conditions regarded as an indication for influenza immunisation by the Department of Health, 228 (27.1%) received vaccine in 1989 - 90 whereas only 7 (2.8%) of the 252 who were not in 'high-risk' groups were immunised ($x^2 = 49.7$, D.F. = 1, $p < 0.05$) indicating that individuals with 'high-risk' conditions are generally targeted. Table 10.3 shows influenza vaccine uptake in 1989 - 90 among 'high-risk' groups as defined by the DoH. There was no significant difference in the proportion of patients in each group who were vaccinated ($x^2 = 13$, D.F. = 7, $p = 0.07$) indicating that no one group was specifically targeted.

The characteristics of vaccinees and non-vaccinees with respect to residential status and level of health as measured by the number of GP consultations during the 12 months before the final illness, number of body systems involved, and number of body systems medicated are shown in table 10.4. Of individuals who lived in residential care 26.9% received

vaccine in 1989 - 90, whereas only 18.1% of those who lived in their own homes were vaccinated.

The independent effects of different variables on the likelihood of influenza vaccination in 1989 - 90 are shown in table 10.5 as odds ratios. Of the following variables: age, sex, residential status (institutional versus community living), number of body systems affected by chronic diseases, number of body systems for which long term medications were prescribed, number of hospital admissions during the 12 months before death, number of hospital admissions during the five years before deaths, and 'previous' influenza immunisation between 1985 - 88, only three variables made significant contribution to the model. Subjects who had seen their GP more frequently during the 12 months before deaths, those who lived in residential care, and those who were previously immunised were significantly more likely to receive influenza vaccine in 1989 - 90.

Year	Cases (n = 315)		Controls (n = 777)	
	Number	Percentage	Number	Percentage
1985 - 86	9	2.9	12	1.1
1986 - 87	17	5.4	32	4.1
1987 - 88	24	7.6	74	9.5
1988 - 89	36	11.4	130	16.7
1989 - 90	57	18.1	178	22.9

Table 10.1: **Influenza vaccine uptake among cases and controls between 1985 - 86 and 1989 - 90.**

Characteristic	Number (percentage)
Age (years)	
16 - 64	46 (4.2)
65 - 74	142 (13)
≥ 75	904 (82.8)
Sex	
Male	347 (31.8)
Female	745 (68.2)
Hospital admissions over last 5 years	
0	667 (61.1)
1 - 5	421 (38.5)
6 or more	4 (0.4)
'High-risk' condition as defined by DoH	840 (76.9)
Non 'high-risk' conditions	252 (23.1)
Influenza vaccine received in 1989/90	235 (21.5)
Influenza vaccine in 1989/90 and previously (1985 - 88)	168 (15.4)

Table 10.2: **Demographic characteristics, health status categorised as high-risk group for whom influenza is recommended, hospital admissions, and vaccination status among the 1092 study subjects**

Patient group	Number (percentage) vaccinated
Cardiac disease	111 (22.1)
COPD and asthma	60 (34.7)
Institutional care	114 (26.9)
Diabetes mellitus	23 (23.7)
Renal disease	4 (21.1)
Other endocrine disorders	10 (20.4)
Other pulmonary disease	3 (20)
Immunosuppression	2 (16.7)

Table 10.3: **Influenza vaccine uptake in 1989 - 90 among 'high-risk' groups as defined by the DoH (groups not mutually exclusive).**

Characteristic	Vaccinees	Non-vaccinees
Median age (years)	85	85
GP visits during 12 months before death		
0	0	49
1 - 10	156	644
11 - 20	58	140
21 - 30	16	22
≥ 30	5	2
Median	7	6
Body systems affected		
0	8	99
1	88	354
2	90	283
3 to 5	49	121
Median	2	1
Body system medicated		
0	41	258
1	117	391
2	63	174
3 to 4	14	34
Median	1	1
Residential status		
Residential	114	310
Non-residential	121	547
Total	235	857

Table 10.4: **Health, age and residential status of vaccinees and non-vaccinees in 1989 - 90.**

Factor	Odds ratio of vaccination in 1989 - 90 (and 95% confidence interval)
GP visits during the 12 months before death	1.04 (1.03 - 1.04)
Residential care	1.45 (1.17 - 1.79)
Previous vaccination (1985 - 1988)	7.61 (6.06 - 9.56)

Table 10.5: **Factors affecting influenza vaccine uptake in 1989 - 90 among the 1092 study subjects.**

10.3 Discussion

The groups included in this study represent the full range of patients for whom vaccination is recommended by the DoH (Department of Health, 1992). Because all subjects in this study died either during the 1989 - 90 epidemic or the following winter, the sampling undoubtedly selected individuals whose health was especially poor; more than three quarters had a condition regarded by the DoH as a risk factor for influenza complications and death. The nature and severity of illness in the subjects studied has put them in regular contact with their general practitioners. It is noteworthy that more than 95% of all subjects had been seen by a family doctor on at least one occasion during the last 12 months before death. Most individuals in this study who did not receive vaccine can, therefore, be regarded as examples of 'missed immunisation'.

Overall only 235 of 1092 (21.5%) individuals received influenza vaccine in the 1989 - 90 season. The level of vaccination was higher in those with 'high-risk' conditions as compared with those who were not in 'high-risk' groups ($x^2 = 49.7$, D.F. = 1, $p < 0.05$) indicating that patients with 'high-risk' are targeted. Similar proportions of patients in each 'high-risk' chronic illness category as defined by the DoH received vaccine indicating that no specific group was targeted. However, there is a suggestion towards a higher level of immunisation in patients with COPD and asthma; patients with immunosuppression were the most poorly targeted.

Also there seems to be targeting in that residential care patients and those who were 'previously' vaccinated were more likely to receive vaccine in 1989 - 90. It may also be possible that patients with more severe chronic disease, as measured by the number of GP visits during the 12 months before death, are specifically targeted. However, this may represent different patterns of care or may indicate that vaccine is given opportunistically following medical consultations. Two surveys

conducted in Leicester showed that more than three quarters of vaccinees were offered vaccine at the surgery during consultations with GP or practice nurse (Nguyen-Van-Tam and Nicholson, 1993; Nicholson, 1993). Of the people who did not receive vaccine in this study, more than 90% had seen their GP at least on one occasion during the 12 months before death. This shows clearly that a number of opportunities to encourage vaccine uptake were missed. The finding that 'previous' vaccinees (between 1985 - 88) were more likely to receive immunisation in 1989 - 90 is encouraging as it indicates that these individuals tolerated vaccine well and apparently had no objection to repeat annual vaccination.

In spite of the high prevalence of 'high-risk' medical conditions in the subjects included in this study, they were evidently managed mostly at the primary care level. This emphasises the important role that primary care has to play in delivery of vaccine. The study did not include data on the number of visits to hospital out-patient departments as GP records do not document this. Nevertheless about 40% of individuals studied had been admitted to hospital and conceivably most had been seen on one or more occasions in out-patient departments. In addition, patients with more severe chronic medical conditions might have been referred and followed-up in medical out patient clinics because of difficulties in controlling illness. For these individuals, efforts to encourage vaccine uptake in these settings could be rewarding. However, a survey in Trent has shown that only about 7% of patients received advice about vaccine from hospitals (Nguyen-Van-Tam and Nicholson, 1993).

Nguyen-Van-Tam and Nicholson, (1993) found that 95% of vaccine offers were made at primary care levels. However, very little information exist in the UK on how 'high-risk' groups are identified. Target groups could be identified in general practices by using age and chronic disease registers, but only general practices with computerised practice register

would be able to do this. A recent survey of general practices has shown that 80% possess at least one computerised practice register (Nguyen-Van-Tam and Nicholson, 1993).

Although more than 95% of individuals in this study were 65 years or over, the sampling technique has selected people with poor health. Therefore, the prevalence of medical conditions, in both cases and controls, regarded as an indication for vaccination (76.9%) in those of the same age group is likely to be less. Nicholson, (1993) found that 170 of 335 (51%) of all individuals aged 65 years or over living at home had one or more medical indications for immunisation. However Nicholson's data were collected using a postal survey and people without severe medical conditions may have failed to respond resulting in spuriously high prevalence. Conversely, people with 'stable' chronic medical conditions (e.g. those with a prior myocardial infarct) who are symptom free and are taking no medication, may not appreciate that they have a risk-factor. A recent survey in the UK. has shown that about 63% of all individuals 65 years or over suffer from a long standing illness (Central Statistical Office, 1996). However, some of these illnesses may not be among 'high-risk' conditions for which vaccination is recommended by the DoH.

Offers of vaccine could be attached to repeat prescriptions. Overall 793 (73%) individuals in this study had chronic illnesses for which medications were prescribed, however, some of these illnesses may not have been among those for which influenza vaccination is indicated.

CHAPTER 11

Fatal influenza cases: chronic ill-health and details of final illness

11.1 Introduction

Influenza epidemics are regularly associated with increased winter mortality. In the United States it has been estimated that from 1971-72 through 1977-78 influenza resulted, on average, in 16,000 excess deaths annually (Riddiough, 1983). Total influenza-associated excess mortality in six epidemics from the winter of 1972/73 to 1980/81 was about 200,000 (Riddiough, 1983). In England and Wales about 120,000 excess deaths were attributed to influenza during the ten winters after influenza A/Hong Kong (H3N2) first arrived in 1968 - 69 (Tillett *et al.*, 1983). The 1989 - 90 epidemic was the worst to have hit Britain since 1975 - 76 causing about 30,000 excess deaths (Ashley *et al.*, 1991).

In the UK. remarkably little is known about the previous health status of those dying from influenza. For example, it is unclear whether influenza deaths occur exclusively in individuals over 65 years with chronic ill-health or whether a sizeable proportion occurs in those aged over 65 who previously enjoyed good health. Clearly such knowledge could affect vaccination strategies.

During the 1918-19 influenza pandemic the mortality curve was W-shaped with high fatality in young adults and at the extremes of age. A striking feature of the pandemic was the high case-fatality rate; about 50% of those aged 20 to 40 years who developed pneumonia died (Ministry of Health, 1920). The course of illness in these cases was fulminant and patients died very quickly from respiratory failure (Grist, 1979). Although case-fatality rates were variable during the several influenza epidemics that followed, the course of final illness in some fatal influenza cases was comparable to the pandemic in 1918-19 (Stuart-Harris *et al.*, 1985). For

example, Oseasohn *et al.*, (1959) described clinicopathological features of 33 influenza patients who died during the 1957 epidemic in Cleveland, USA. In spite of the low case-fatality rate during the epidemic, they found that the most striking features of those who died was the fulminant course of illness. Similar observations were noted in the report by the Public Health Laboratory Services in deaths from Asian influenza, 1957 (Public Health Laboratory Services, 1958).

Little information exists on the course of illness in patients who died of influenza during the 1989-90 epidemic. Undoubtedly medical management has improved since earlier epidemics but it is unclear whether this has changed the course of illness. Such information might also be of importance in influencing vaccination strategies. The following analysis deals with details of chronic ill-health and final illness in 315 fatal influenza cases who died during week 44, 1989, to week 8, 1990.

11.2 Results

A total of 412 fatal influenza cases were identified in 36 Health Authorities in England; general practitioners' records were available for 315. Figure 11.1 shows frequency distribution of general practitioners' consultations during the final illness. The median number of general practitioner consultations was two. Eighty-seven percent of fatal cases were seen by their general practitioners at least on one occasion during the final illness and 6% were seen five times or more. Table 11.1 shows the number admitted to hospitals and drugs prescribed during the final illness for the 315 fatal influenza cases. New drugs were prescribed by general practitioners during the final illness for 233 (74%) of all fatal influenza cases. More than 80% (192 of 233) of those prescribed drugs were given antibiotics, whereas 16% (37 of 233) were prescribed pulmonary medications and only 6% (13 of 233) cardiovascular medications.

Figure 11.2 shows the interval between onset of illness and death for 275 fatal cases. The median duration of final illness was seven days. Seventeen percent died within 48 hours of onset of final illness. Sixty-four percent died within 7 days of onset of illness - that is in the acute influenza stage; only one patient lived for more than 7 weeks after onset of final illness.

Figure 11.3 shows interval between admission to hospital and death for 35 patients (data on date of hospital admission were missing for 19 patients). Forty-six percent of those admitted died within 48 hours of admission. More than three quarters of patients died within seven days of admission. Only one patient was in hospital for more than 7 weeks.

Table 11.2 shows the primary and contributory causes of death for the 315 cases. More than 85% of cases had influenza mentioned as the cause directly leading to death or leading to the disease causing it (i.e. Ia, and Ib). Influenza was certified as the principal cause of death (i.e. Ia) for 76 (24.1%) cases; 34 (44.7%) of these cases had cardiovascular disease, 7 (9.2%) had pulmonary disease, and 4 (5.3) had neurological disease as contributory causes. Two hundred and seven (65.7%) of the fatal influenza cases had pneumonia during the final illness; in 192 (60.9%) cases this directly led to cause of death (i.e. Ia), and in 15 (4.8%) it was a contributory cause.

Of the 207 fatal influenza cases who had pneumonia during the final illness 17 (8.2%) had no chronic disease whereas 190 (91.8%) suffered from one or more chronic medical conditions before death. Table 11.3 shows the incidence of pneumonia among different patient groups of the 315 fatal influenza cases. There is no significant difference in the proportion of patients in each group who developed pneumonia ($x^2 = 3.8$, D.F. = 5, p = 0.58).

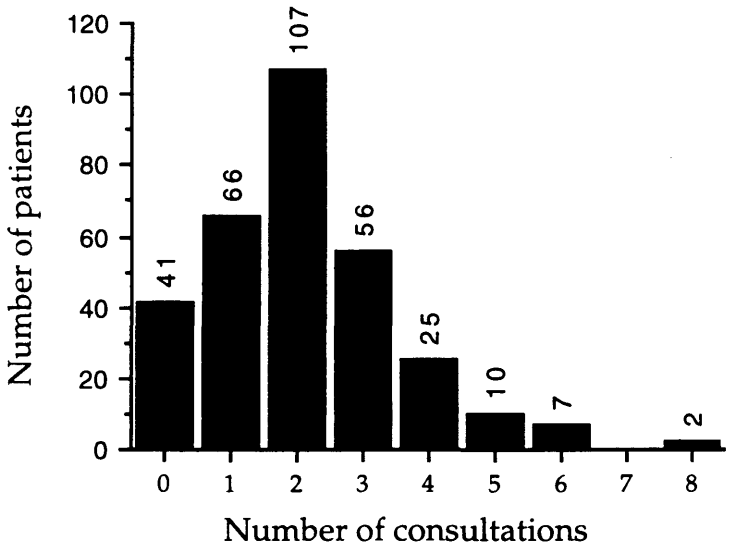

Figure 11.1: **Frequency distribution of general practitioners' consultations during the final illness for fatal influenza cases (data missing for one patient).**

Characteristic	Number (percentage)
Admitted to hospital	
Yes	54 (17)
No	261 (83)
Drugs prescribed by general practitioner	
Yes	233 (74)
No	42 (13)
Missing information	40 (13)
Antibiotics	192 (61)
Pulmonary medication	37 (12)
CVS medication	13 (4)

Table 11.1: **General practitioner consultations, hospital admissions, and drugs prescribed during final illness of cases.**

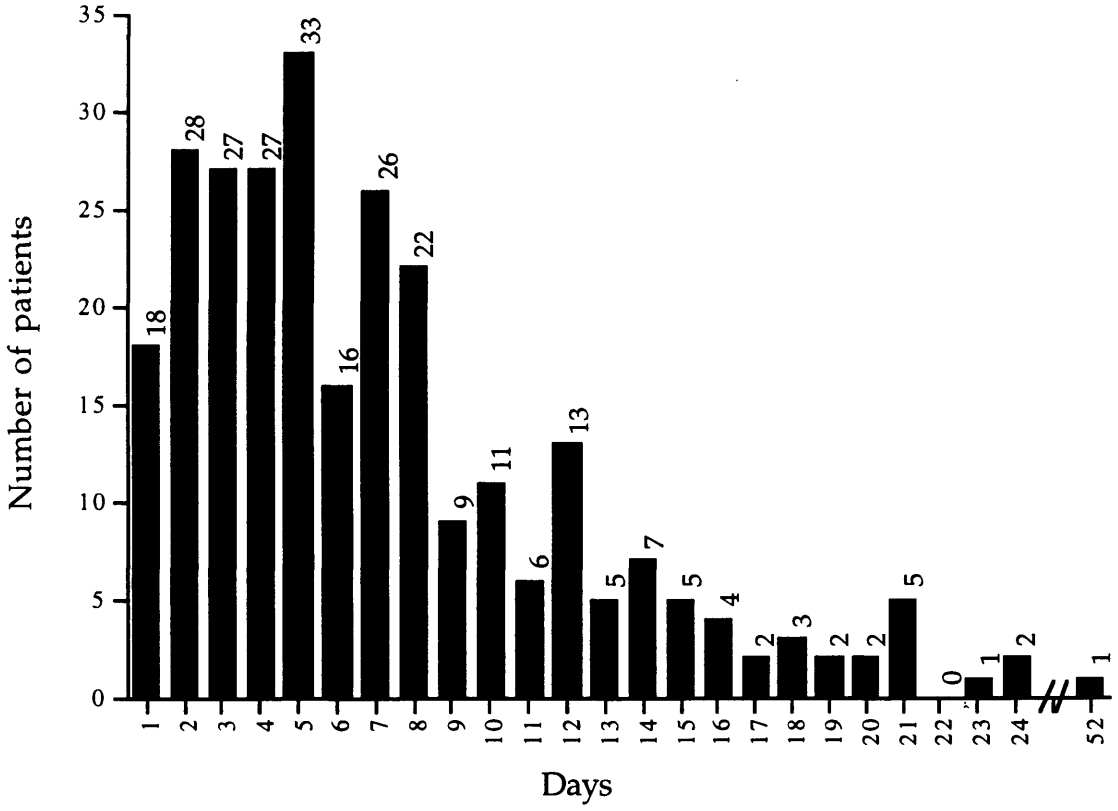

Figure 11.2: **Interval between onset of illness and death of cases (data missing for 40 patients).**

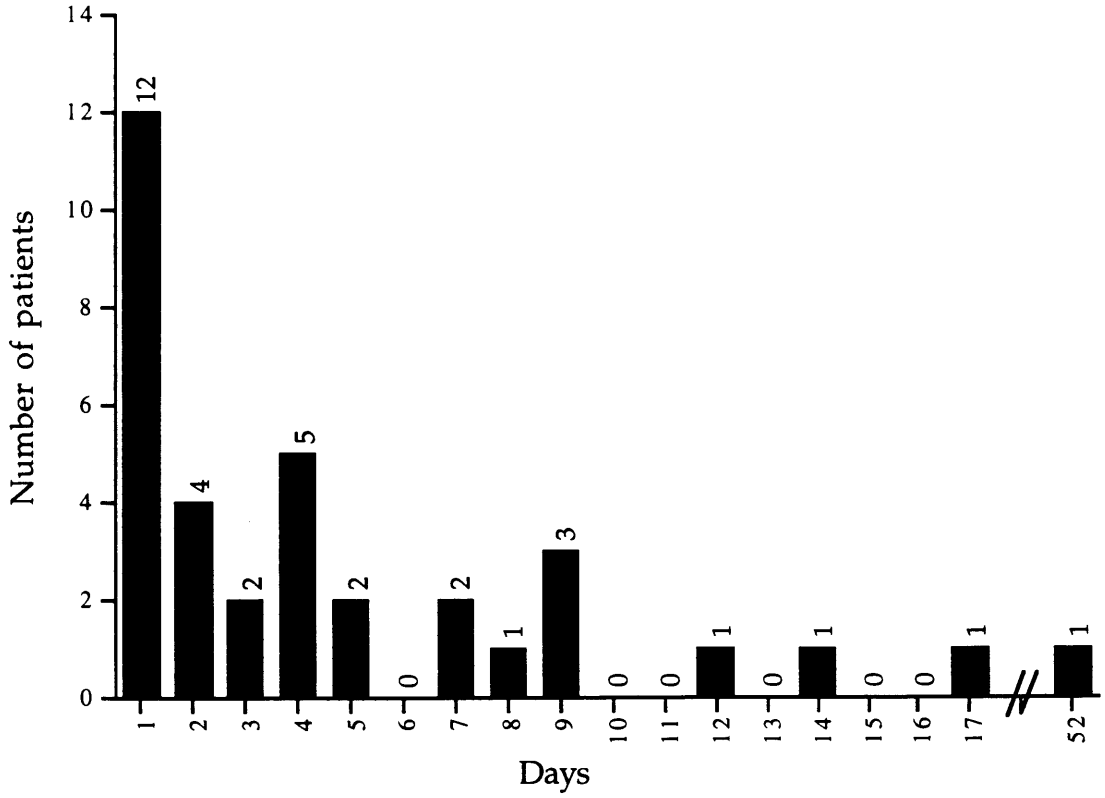

Figure 11.3: **Interval between admission to hospital and death of cases (data missing on date of hospital admission for 19 patients).**

Cause of death	Ia	Ib	Ic	II
Influenza	76	200	19	20
Pneumonia	192	14	1	0
Cardiovascular disease	34	21	8	30
Pulmonary disease	7	6	10	16
Neurological disease	4	3	2	52
Diabetes mellitus	0	1	1	9
Renal disease	0	0	1	1
Malignancy	0	0	0	4
Old age	1		1	12
Infection (other than pneumonia)	1	2	0	0
Musculoskeletal and connective tissue disease	0	0	1	6
Others	0	2	1	15
No cause mentioned	0	65	270	150
Data not legible	0	1	0	0

Table 11.2: **Cause of death for the 315 cases.**

Ia = Directly leading to cause of death.

Ib = Directly leading to 1a.

Ic = Directly leading to 1b.

II = Other conditions contributing to the death, but not related to the disease causing it.

Patient group	Number (percentage) who developed fatal pneumonia
Pulmonary disease	43 (60.5)
Cardiac disease	76 (58.5)
Neurological disease	84 (68.9)
Diabetes	15 (62.5)
Other endocrine disease	15 (68.2)
Renal disease	3 (50)

Table 11.3: **Incidence of pneumonia among the 315 fatal influenza cases during the 1989 - 90 influenza epidemic (groups not mutually exclusive).**

11.3 Discussion

The 315 fatal influenza cases included in this analysis may not have been a randomly selected sample, but they represent about 13% of all individuals whose death was certified as due to influenza in England during the 1989-90 epidemic (Ashley *et al.*, 1991). The sample was collected from 36 Health Authorities extending over five Health Regions with a total population of about 10 million. The distribution of these cases in time agreed well with other indices of influenza activity (figure 9.1). Therefore, this sample may be regarded as representative of fatal influenza cases in England during the 1989-90 epidemic. However, since no virologic confirmation was obtained some deaths in which influenza played no part may have been included.

The observation that almost all certified influenza deaths were in individuals 65 years or older (table 9.2) is in agreement with previous influenza mortality patterns for England and Wales. During the 15 years 1974 - 88 the lowest mean mortality for deaths certified as due to influenza (0.04/100,000) occurred in 5 to 14 year olds; mortality increased in successive 10 year age bands by three-fold, four-fold, six-fold, 11-fold 32.5-fold, 100-fold, and 765-fold to a mean of 30.6/100,000 in those aged 75 years or over. (World Health Organisation Statistics Annuals, 1977-89). The finding that only 52 of the 315 (16.5%) of fatal influenza cases were among people who were not among 'high-risk' groups as defined by the DoH is in agreement with two studies from Oregon, USA and Leicestershire, UK. (Barker and Mullooly, 1982; Nguyen-Van-Tam and Nicholson, 1992).

Clearly the great majority of deaths occurred in those 65 years or over with chronic ill-health. Therefore, the results of this study do not provide a strong argument to extend the current immunisation policy to include all individuals 65 years or over as this would have little impact of certified influenza death. A recent survey has shown that only 63% of

those 65 years or over have long standing illness and fewer may have conditions currently regarded as being 'high-risk' for the complications of influenza (Central Statistical Office, 1996). Furthermore, the elderly population in the UK. is large. Those 65 years or over constitute about 16% of the total population (Central Statistical Office, 1996), and the number of those over 75 years is projected to increase by almost 10% during the next decade (OPCS Monitor PP2 89/2, 1989). Therefore implementation of such policy may not be cost-effective. However, it could be argued that influenza in the elderly without 'high-risk' can lead to considerable morbidity and GP visits, antibiotic prescriptions, and that after all may be cost-effective. Clearly a carefully designed community based cost-effectiveness study is warranted to address this issue.

For final illness the most remarkable feature is the rapid deterioration following onset. Almost two-thirds of patients died in the acute influenza stage, i.e., within the first seven days of onset. This is in agreement with observations noted during earlier epidemics. A report by the Public Health Laboratory Services on 477 fatal influenza cases during the 1957/58 epidemic showed that about 70% of patients died during the first seven days after the onset of illness (Public Health Laboratory Services, 1958). At least 74% of the 315 fatal influenza cases received medication during the final illness. In these cases this clearly failed to prevent death. It is, however, conceivable that treatment was given too late to influence outcome in many of these patients. Of the patients who were admitted to hospital and whose time to death is known (35 patients) almost half died within the first 48 hours after admission. This indicates that more aggressive hospital treatment failed to alter outcome in these patients. However, these patients may have been ill for a long period of time before admission.

The association of pneumonia with influenza was well documented during the 1918 pandemic and more recently (Ministry of Health, 1920; Oseasohn *et al.*, 1959; Stuart-Harris *et al.*, 1985). The incidence of pneumonia complicating influenza ranges from about 3% in primary care setting to 11% among residential patients (Connolly *et al.*, 1993; Strassburg *et al.*, 1986). In this study, however, 207 of the 315 (66%) fatal influenza cases developed pneumonia during the final illness. This rate is similar to rates noted during post-mortem examinations. Oseasohn *et al.*, 1959 reported 33 fatal influenza cases, 14 (43%) of whom were found to have pneumonia at post-mortem examination. A report by the Public Health Laboratory showed that among 219 fatal influenza cases for whom post-mortem records were available 85% had pneumonia (Public Health Laboratory Services, 1958).

The overwhelming majority, about 80%, of patients with pneumonia admitted during influenza epidemics suffer from one or more underlying chronic diseases (Schwarzmann *et al.*, 1971). However, no data are available in the relative importance of these diseases to the development of pneumonia. This study has shown that the complication of pneumonia is as common in those who die from influenza, who have chronic pulmonary disease, as those with cardiac, neurological, diabetes, other endocrine, or renal diseases.

Overall at least 74% of fatal influenza cases received medications, mostly antibiotics. It is impossible to say whether various methods of treatment that failed in these patients were successful in others as this study includes only the failures. However, influenza and its attendant complications may take a rapidly fatal course that death supervenes within a few days from the beginning of illness. In such cases the opportunity to institute effective therapy is precluded by shortness of the

illness. This lends further support for vaccination as the most effective means for reducing this type of mortality.

Hospital Admission Study

CHAPTER 12

Influenza vaccine effectiveness in reducing admissions and risk factors for hospitalisation

12.1 Introduction

Influenza epidemics are regularly associated with an increase in admissions for acute respiratory disease. In the United States it is estimated that influenza epidemics are associated with more than 170,000 excess hospitalisations annually (Barker, 1986). During a survey of acute respiratory disease hospitalisations (*ICD-9-CM* codes 460 - 466 or 480 - 487) during the period 1978 - 1981, Perrotta *et al.*, (1985) examined 13,297 discharge records in 11 hospitals in Houston, USA. These investigators found a strong correlation between acute respiratory disease hospitalisations and virologically determined influenza epidemic curves ($r = 0.74$), with the peak of hospitalisations lagging one week behind peak virus-positive illnesses in sentinel clinics (Perrotta *et al.*, 1985). In Texas, USA, during the 1976 epidemic the age specific rates for hospitalisation were equally high for infants and those 65 years of age or older: about 1.6% of individuals in each age group were hospitalised (Glezen, 1982). Between 1970 - 78 the mean excess rates for hospital admissions increased with age, and were 35, 93, and 370 per 100,000 persons per epidemic for age groups 15 - 44, 45 - 64, and 65 years or older respectively (Barker, 1986). Beside age the risk factors for acute respiratory disease hospitalisation of adults include diabetes mellitus, chronic pulmonary, and cardiac disease (Glezen *et al.*, 1987; Bouter, 1991). Glezen *et al.*, (1987) also showed that the highest rate of hospitalisation during influenza epidemics (875 per 100,000) occurred among persons older than 65 years with underlying chronic pulmonary disease; chronic cardiac disease represented the second

most frequent disorder of adults hospitalised for acute respiratory disease (502 per 100,000).

Many studies have reported influenza vaccine effectiveness in reducing influenza related morbidity. A meta-analyses of 16 studies in the elderly revealed that influenza vaccine reduced morbidity by 23% (95% CI 5 - 37%) (Strassburg *et al.*, 1986). The shortcomings of such studies are well recognised: none was randomised, all except three involved residential care with no distinction between those with and without chronic diseases and the possibility that vaccine was withheld from patients with poor life quality, or that medical management of sick non-vaccinated subjects was different to vaccinees can be excluded.

The epidemic of influenza A/England/308/89 (H3N2), which occurred during the winter of 1989/90, provided the opportunity to study vaccine effectiveness in Leicestershire in reducing hospital admissions for pneumonia, influenza, emphysema, or bronchitis during a period when vaccine and wild strains were well matched. The findings are reported below.

12.2 Results

Three hundred and three admissions to Leicestershire hospitals whose primary discharge diagnosis or cause of death was either influenza, pneumonia, emphysema, or bronchitis were identified. In-patient records were successfully retrieved for 264 admissions (87.1%). Figure 12.1 shows the temporal relation between the 264 admissions and consultation rates for epidemic influenza and influenza-like illness as reported by the Royal College of General Practitioners' sentinel practices. For 156 of these admissions (the cases) (59.1% of the 264 and 51.5% of the 303 admissions), we were able to access the primary care records and matched 289 controls.

Table 12.1 shows the characteristics of cases and controls; 78 of 156 cases (50.0%) died during their stay in hospital and a further 32 (20.5%) during the following nine months. Twenty seven of 156 cases (17.3%) received influenza vaccine in 1989 compared to 69 of 289 controls (23.9%), $X^2 = 1.58$, $p = 0.11$; this gave an odds ratio of hospital admission among vaccinees of 0.67 (95% CI 0.39 - 1.12), and vaccine effectiveness could be estimated at 33% (95% CI 0 - 61%). Based on the final conditional logistic regression model, table 12.2 shows the risk of hospital admission for influenza, pneumonia, emphysema, or bronchitis associated with various chronic conditions. Each risk is adjusted for all of the other variables in table 12.2 and for current and previous vaccination. The risk of hospital admission was significantly increased among individuals with chronic pulmonary disease and those living in residential care. However, patients with musculoskeletal or connective tissues disorders were less likely to be admitted. Overall the risk of admission for patients in the high-risk groups specified by the DoH (Department of Health, 1992) was more than doubled.

The risks associated with the two types of vaccination status are shown in table 12.3, each being adjusted for the other, and all of the chronic conditions shown in table 12.2. Current influenza vaccination made a significant contribution to the model after adjustment for the effects of the other variables ($p = 0.011$). The use of influenza vaccine in the 'current' season reduced the likelihood of hospital admission by 63% (95% CI 17-84) whereas 'previous' vaccination offered no protection. The interaction between current and previous vaccination status was examined but not found to be significant ($p = 0.82$). Furthermore, no significant interactions were found between the effect of vaccine in subjects with high-risk conditions and those without ($p = 0.23$) and between subjects living in residential care and those in their own homes

($p = 0.88$). However, there was a marked trend towards enhanced vaccine effectiveness among subjects living in residential care compared to the open community (V_E: 70% (95% CI 32 - 87) versus 19% (95% 0 - 82).

Table 12.4 shows age and level of health as measured by number of body systems affected by chronic disease and number of body systems for which long term medications were prescribed of cases who died in hospital or soon after discharge and those who survived. Cases who died in hospital were older (median age 82 years versus 67.5 years; two sample *t*-test = 8.8, D.F. 154. $p < 0.001$), had more body systems affected by chronic illness (mean 1.6 versus 1; $X^2 = 16.5$, D.F 3, $p = 0.001$), and more body systems for which regular medications were prescribed (mean 1.1 versus 0.9; $X^2 = 11.0$, D.F. 3, $p = 0.012$).

Figure 12.2 shows the duration of hospitalisation before death for those who died in hospital. The median duration of hospitalisation was 5 days (range 1 - 54 days). More than one third died within two days of hospitalisation, and less than one third survived for more than eight days.

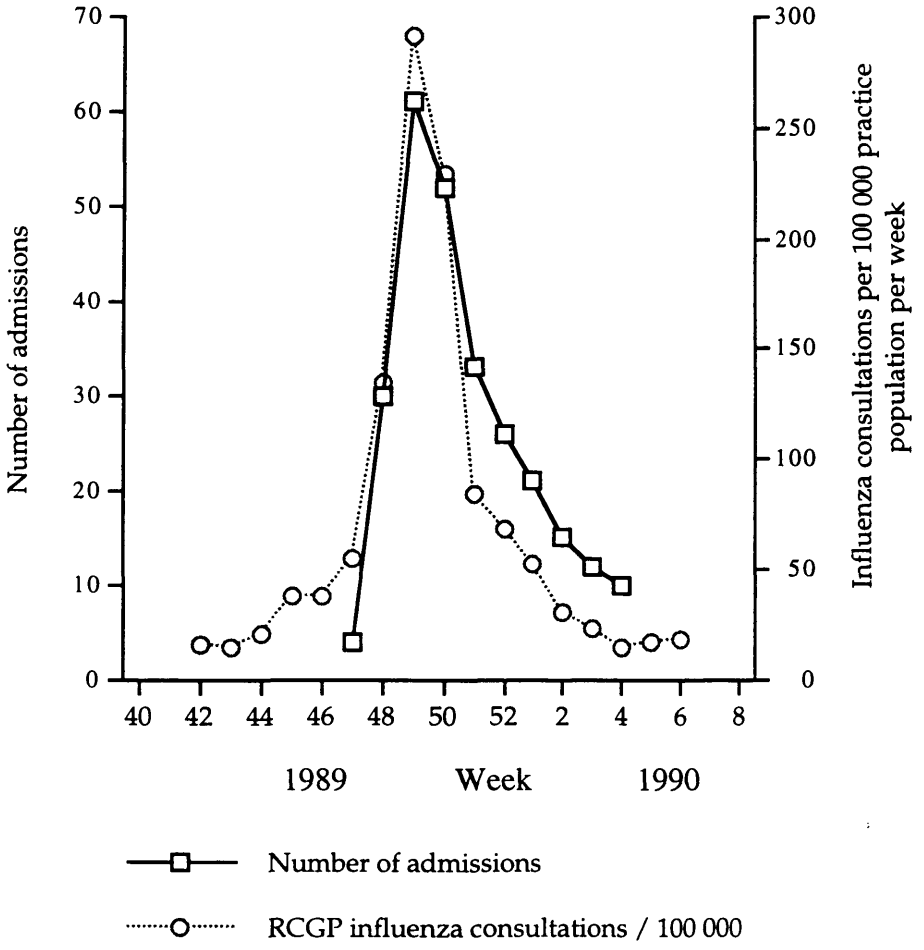

Figure 12.1: **Temporal relation between admissions for influenza, pneumonia, emphysema, or bronchitis in Leicestershire and consultation rates for 'influenza' in sentinel practices.**

Characteristic	Number (percentage) Cases n = 156	Controls n = 289
Age in years		
16 - 44	13 (8.3)	26 (9.0)
45 - 64	13 (8.3)	22 (7.6)
65 - 74	30 (19.2)	53 (18.3)
75 - 84	56 (35.9)	105 (36.3)
85 - 94	38 (24.4)	73 (25.3)
≥ 95	6 (3.8)	10 (3.5)
Sex:		
Male	72 (46.2)	132 (45.7)
Female	84 (53.8)	157 (54.3)
Residential status		
Institution*	24 (15.3)	25 (8.7)
Community	132 (84.6)	264 (91.3)
Chronic diseases:		
Heart disease*	70 (44.9)	125 (43.3)
Chronic pulmonary disease*	47 (30.1)	43 (14.9)
Renal disease*	2 (1.3)	10 (3.5)
Diabetes*	17 (10.9)	20 (6.9)
Other endocrine disease*	6 (3.8)	9 (3.1)
Immunosuppression*	1 (0.6)	5 (1.7)
Malignancy	14 (9.0)	37 (12.8)
Neurological disease	23 (14.7)	46 (15.9)
Musculoskeletal and connective tissue disease	13 (8.3)	49 (17.0)
Other chronic illness	35 (22.4)	66 (22.8)
Influenza vaccine recommended by DoH		
Yes	113 (72.4)	171 (59.2)
No	43 (27.6)	118 (40.8)
Influenza vaccine received		
1989 only (current)	4 (2.6)	21 (7.3)
1985 - 1988 only (previous)	9 (5.8)	8 (2.8)
Both	23 (14.7)	48 (16.6)
Neither	120 (76.9)	212 (73.4)

* DoH designated high-risk group.

Table 12.1: **Demographic characteristics, chronic diseases and residential status of cases and controls.**

Factor	Odds Ratio for hospital admission	95% confidence interval
Institutional care*	2.96	1.35 - 6.53
Chronic pulmonary disease*	2.63	1.59 - 4.35
DoH high-risk groups combined*	2.04	1.29 - 3.25
Diabetes mellitus*	1.48	0.66 - 3.34
Cardiac disease*	1.20	0.74 - 1.94
Other endocrine disorders*	0.98	0.27 - 3.58
Neurological disease	0.94	0.52 - 1.70
Immunocompromised*	0.73	0.08 - 6.91
Malignancy	0.63	0.29 - 1.36
Musculoskeletal/connective tissue disease	0.42	0.21 - 0.85
Renal disease*	0.52	0.11 - 2.51

*DoH designated high-risk groups

Odds ratios for hospital admission adjusted for all other variables in table, and for current and previous influenza vaccination.

Table 12.2: **Risk factors for admission with influenza, pneumonia, emphysema or bronchitis during the 1989/90 influenza A epidemic in Leicestershire, UK.**

Status	Odds ratio for hospital admission (95% CI)	% V_E (95% CI)
Previous vaccination (1985 - 1988)	2.25 (1.00 - 5.09)	0
Current vaccination (1989)	0.37 (0.16 - 0.83)	63 (17 - 84)

Odds ratio for each vaccination status adjusted for the other, and for all chronic conditions in table 12.2.

Table 12.3: **Effectiveness of current and previous influenza vaccination (V_E) in preventing hospital admissions during the 1989/90 influenza epidemic in Leicestershire, UK.**

Characteristic	Died in hospital or up to nine months after discharge	Survived
Age median (range)	82 (21 - 99)	67.5 (16 - 89)
Body system affected by chronic disease		
Mean (standard deviation)	1.6 (0.95)	1 (1.05)
0	12	17
1	45	18
2	35	7
3 to 4	18	4
Body system for which long term medications was prescribed		
Mean (standard deviation)	1.1 (0.79)	0.9 (0.96)
0	23	18
1	54	21
2	28	3
3 to 4	5	4
Total	110	46

Table 12.4: **Age and health status of cases who died (in hospital or soon after discharge) and survivors.**

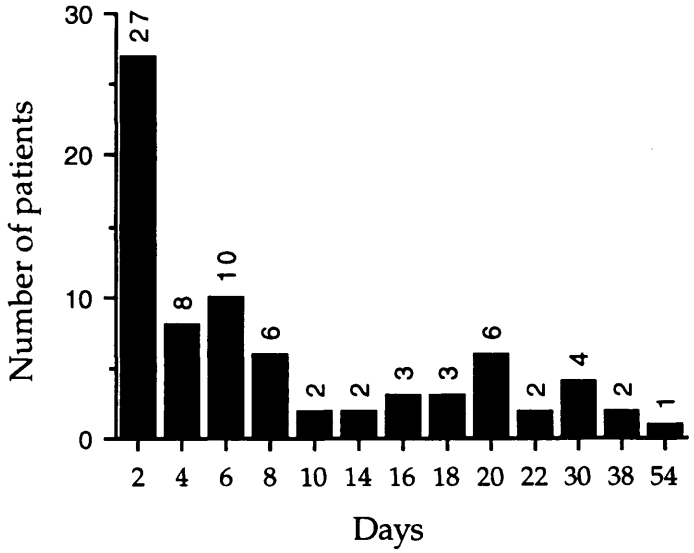

Figure 12.2: **Interval between admission to hospital and death during admissions (data missing for two patient).**

12.3 Discussion

Study design

The outcome used in this study was hospitalisation for pneumonia, influenza, bronchitis or emphysema, it was not possible to establish whether any of these admissions were actually the result of influenza. However, The 1989/90 epidemic resulted in the highest laboratory reporting of influenza since 1975/76 and acute respiratory disease hospitalisation in adults has been shown to closely match influenza epidemic curves for virus reports (Glezen *et al.*, 1987). Furthermore, the study period coincided with peak clinical activity, and hospital admissions in Leicestershire closely mirrored Royal College of General Practitioners consultation rates in sentinel practices (figure 12.1). Despite a strong association between acute respiratory disease hospitalisation and virus isolation during major epidemics, as in 1989 - 90, it is still probable that cases were included which were not actually caused by influenza. The effect of this misclassification bias would be to underestimate vaccine effectiveness, so the estimate in the present study is again probably conservative.

The major source of bias in this study stems from the non-availability of primary care records in almost 50% of the cases that were originally identified, although hospital records were available for almost 90%. It may be the case that general practitioners who did not operate an active policy of influenza immunisation in 1989 - 90 were less likely to give their permission for us to access the notes of patients who were admitted. Thus the level of vaccine uptake measured among cases may, if anything, have been spuriously high resulting in an underestimation of vaccine effectiveness.

Another possible limitation of the study is its reliance on the documentation of vaccination status. Virtually all influenza vaccine is

prescribed and administered by patients' general practitioners in the UK, and its administration has potential medico-legal implications. Under-recording of vaccination is thus likely to have been infrequent and no more likely to have occurred among cases than controls, therefore having no appreciable effect on estimates of vaccine effectiveness. The vaccine uptake of 23.9% among controls in the present study is similar to the uptake, described in other studies in England that took place around 1989/90 involving reviews of medical records or self-reporting (Nicholson *et al.*, 1987; Nguyen-Van-Tam and Nicholson, 1993). Moreover the immunisation rate of 17.3% among cases in this study is very close to the rate (18.1%) found in 36 district health authorities in England during 1989/90 among 315 fatalities with influenza as noted in the mortality study (Chapter 9).

Mortality statistics indicate that influenza epidemics can hasten the deaths of many people whose underlying illness would be fatal in the ensuing months (Eickhoff *et al.*, 1961; Ashley *et al.*, 1991). Accordingly for cases who died in hospital or shortly after discharge, controls were chosen from individuals who died shortly after the epidemic. Although overall 32.6% (86/264) of cases died during admission, the mortality rate among the cases we studied (50.2% during hospitalisation and an additional 20.5% during the 9 months thereafter) was very high; this reflects the greater availability of information on people who died. Those who died during admission or soon after discharge were elderly patients with high prevalence of severe chronic ill-health as measured by number of body systems for which long term medications were prescribed; these are the individuals among whom influenza mortality is increased. This suggests that we focused on a debilitated population and introduced an element of potential bias. Notwithstanding, the validity of the study design is supported by showing that institutional care and chronic pulmonary

disease as independent risk factors for hospitalisation. As in the mortality study the recognised risk factors chronic heart disease, diabetes mellitus, and renal disease were not confirmed individually, possibly because they were important factors contributing to the deaths of controls, or because of the small numbers studied. Nevertheless, the study showed that the risk of admission among groups for whom the DoH strongly recommends vaccination (Department of Health, 1992) was significantly increased. The identical observation was found with respect to deaths in the mortality study.

Besides comorbidity, previous pneumococcal vaccination might have modified an individual's risk from influenza complications. Virtually no pneumococcal vaccine was distributed among high-risk subjects in the UK during the study period and preceding 5 years as noted in the mortality study, so it is very unlikely that pneumococcal vaccination had any effect on the likelihood of hospitalisation among those studied.

Risk Factors for admission with acute respiratory diseases

The study has shown that COPD is an important independent risk factor for admissions with influenza, pneumonia, bronchitis and emphysema during a period of peak influenza activity. This is in agreement with previous studies adopting data from epidemiological surveys (Glezen *et al.*, 1987), and a recent case-control study (Foster *et al.*, 1992). People who live in residential care were almost three times more likely to be admitted for acute respiratory disease during the 1989 - 90 influenza A epidemic. Although no previous study has assessed the risk among residential care individuals for hospital admissions, this in agreement with a study reported by Nguyen-Van-Tam and Nicholson, (1992) showing institutional care to be a risk factor for fatal influenza. However, this

finding can readily be explained by the rapid spread of influenza among a group of debilitated people living in close proximity (Arden *et al.*, 1986), whereas opportunities for transmission are less in non-residential patients with fewer number of contacts with other people.

An interesting finding is that individuals with musculoskeletal and connective tissue disease were less likely to be admitted for influenza, pneumonia, bronchitis and emphysema during the 1989 - 90 epidemic. A similar observation was noted in the mortality study (chapter 9). As discussed previously in chapter 9, it is possible that this protective effect of musculoskeletal disease might have resulted from the use of non-steroidal anti-inflammatory medications which, by acting as prostaglandin inhibitors, significantly increase the proportion of subjects with a 4-fold rise in antibody against influenza A following vaccination (Hsia, 1994). Another possibility is that non-steroidal anti-inflammatory drugs might ameliorate the illness. Clearly this is an area where more research is needed.

Vaccine effectiveness in reducing hospital admissions

This analysis demonstrated significant vaccine effectiveness in reducing hospital admissions for influenza, pneumonia, bronchitis and emphysema during a period of peak influenzal activity. The findings of this study corroborate the results of observational studies (Arden *et al.*, 1986; Gross *et al.*, 1995) as well as recent North American cohort and case-control studies. Fedson *et al.*, (1993) compared the health and influenza immunisation status of over 5000 non-institutionalised people aged 45 years and over who were admitted to hospitals for lower respiratory tract conditions during two epidemics, with matched controls. Influenza vaccine prevented 32 - 39% of hospital admissions for influenza and pneumonia, and 15 - 34% of admissions for all respiratory conditions.

Foster *et al.*, (1992) reported a similar study among 449 non-institutionalised admissions for pneumonia and influenza aged 65 years or over and 1458 matched controls. Immunisation was associated with a 45% reduction in admissions for pneumonia and influenza. Mullooly *et al.*, (1994) studied vaccine effectiveness over nine influenza seasons in the United States. Vaccine was 30% effective in preventing influenza and pneumonia hospitalisation over the nine years. Nichol *et al.*, (1994) conducted a large cohort study in elderly non-institutionalised individuals over three seasons, 1990/91 to 1992/93, inclusive. Vaccine was 48 - 57% effective in reducing hospitalisation for pneumonia and influenza, 27 - 39% effective in reducing admissions for all acute and chronic respiratory conditions. However, the above studies were all conducted in North America and differences in health care delivery between the US and Britain have made it difficult to apply these findings to the UK.

The study did not examine vaccine effectiveness during a non-epidemic control period, but it did examine effectiveness of vaccine administered during 1985 to 1988, and found no evidence of protection from previous vaccination alone. Conceivably the small number of vaccinees during 1985 to 1988 provided insufficient power to detect small degrees of protection, but the lack of vaccine effectiveness from vaccine given during the years prior to the 1989/90 epidemic was expected since antigenic drift requiring revision of the H3N2 vaccine component occurred in 1989. Moreover the observed lack of effect of prior vaccination during 1989/90 is in agreement with observations noted in the mortality study (Chapter 9).

The mortality study (Chapter 9) showed that influenza vaccine provided a significantly higher level of protection against death among individuals who were repeat (as opposed to first time) vaccinees. The present study failed to show the same difference. Cases were selected on

the basis of hospital admission which partly depends on general practitioner behaviour; the decision to admit to hospital depends on many factors including a belief that hospital treatment would be worthwhile and that the same care could not be provided in the patient's own home. It is therefore possible that well organised practices with established programmes for repeat annual immunisation may also have operated different thresholds for triggering hospital admission than less well organised practices. Other possible explanations are that this might have resulted from the smaller number of patients in the admission study, or that the effect, if real, is only seen in the most debilitated patients.

Reported levels of vaccine effectiveness differ markedly between young and elderly adults. Whereas vaccine offers about 80% protection against influenza-like illness in young individuals (Gundelfinger *et al.*, 1958; Committee on Influenza and other Respiratory Virus Vaccines, 1958), the protection afforded in the elderly is less, about 20% (Arden *et al.*, 1986). However, relatively few studies have considered how the effectiveness of vaccine varies among the elderly. Although failing to reach statistical significance, this study shows a strong trend towards enhanced vaccine effectiveness among the elderly in residential care compared to those living in their own homes. This finding is in agreement with a review by Strassburg *et al.*, (1986) of 30 studies of influenza vaccine in preventing morbidity in the elderly. They found that influenza vaccine was 33% (95% CI 15 to 48%; $p < 0.001$) in reducing morbidity among institutionalised elderly individuals. However, among non-institutionalised elderly vaccine effectiveness was 5% (95% CI -6 to -14%; $p = 0.07$) (Strassburg *et al.*, 1986).

Overall about 70% of the cases included in this analysis died during hospitalisation or the following nine months. The most remarkable feature is the rapid deterioration following hospital admission for many of

the cases. Over two thirds died during the first eight days of hospitalisation. As noted in the mortality study, medical management of these case failed to prevent death, thereby emphasising the importance of vaccination. The finding that vaccine is effective in reducing acute respiratory disease hospitalisations in 'high-risk' patients compared with non-high-risk individuals is in agreement with a study by Mullooly *et al.*, (1994). These investigators studied influenza vaccine effectiveness in reducing hospitalisations over nine influenza seasons. They demonstrated that aggregated influenza vaccine effectiveness in preventing influenza and pneumonia hospitalisations among 'high-risk' elderly was 30% (CI 17% - 42%) whereas effectiveness among non-high-risk elderly was 40% (CI 1% - 64%).

Admissions for acute respiratory conditions are regularly increased during influenza epidemics ((Glezen, 1982; Perrotta *et al.*, 1985)). During the influenza season a 63% (95% CI 17-84) reduction in admissions for acute respiratory illness with concomitant reductions in drug costs could represent a considerable reduction in health costs and reduce the pressure on acute medical admissions. Overall 72.4% of the admissions had 'high-risk' conditions for which influenza vaccine is recommended by the DoH. Thus application of the current UK recommendations might have prevented about 45% of all admissions that occurred, and a similar proportion of deaths.

Considered together, this study, the case-control study on the effectiveness of influenza vaccine in reducing mortality in the UK and similar aforementioned studies in North America provide a solid basis for concluding that despite different health care systems, influenza vaccine has substantial effectiveness in preventing deaths and respiratory complications from influenza. The results of this study support the

current UK guidelines for annual vaccination and the continuing effort to increase vaccine coverage in at-risk groups.

CHAPTER 13

Details and costs of admissions for acute respiratory disease

13.1 Introduction

Influenza epidemics occur almost every year. These epidemics are regularly associated with excess hospital admissions and impose an enormous burden in terms of economic and social costs. In the United States during the period 1971-72 through 1977-78, annual expenditures to treat influenza and its complications averaged about $300 million (Riddiough, 1983). In the UK. during the 1957 epidemic the number of new claims for national insurance sickness benefits was about 2.5 million more than average for the same periods during the previous 5 years (Woodall *et al.*, 1958).

Surveys of adult acute respiratory disease hospitalisations have shown strong correlation with virologically determined epidemic curves (Glezen, 1982; Perrotta *et al.*, 1985). A major goal for influenza vaccination policy is reduction in influenza associated excess morbidity and mortality. While excess mortality due to epidemic influenza has been measured in the UK (Ashley *et al.*, 1991), excess hospitalisations, which probably represent the largest cost to the national health service, have not been analysed. There is good evidence now, as shown in Chapter 12 and similarly designed North American studies (Foster *et al.*, 1992; Fedson *et al.*, 1993; Mullooly *et al.*, 1994; Nichol *et al.*, 1994), that influenza vaccine offers about 50% reduction in admissions for influenza and pneumonia among the elderly during epidemic periods. The costs of these admissions is unknown, as is the economic benefit that may be derived from vaccination in the UK. Therefore, it becomes important for policy-making purposes to measure the economic impact of this excess. This report describes the hospitalisation details and costs of 264 patients admitted to

Leicestershire hospitals for influenza, pneumonia, emphysema, or bronchitis during the 1989 - 90 influenza epidemic.

13.2 Results

Three hundred and three admissions to 15 Leicestershire hospitals whose primary discharge diagnosis or cause of death was influenza, pneumonia, emphysema, or bronchitis (*ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492) during the period December 1, through January 31, 1989-90 were identified. Table 13.1 shows the number and percentage of patients with these diagnoses. Table 13.2 shows the number and percentage of patients admitted to each of the 15 hospitals in Leicestershire. More than 80% of patients were admitted to teaching hospitals. Figure 13.1 shows the number of admissions with influenza, pneumonia, emphysema, or bronchitis (*ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492) during the period December 1, through January 31, in the years 1987-88, 1988-89, 1989-90 and 1990-91. The number of admissions in 1989-90 increased by 42% in comparison with the mean number of admissions during the corresponding period in 1987-88, 1988-89, and 1990-91. Based on a Leicestershire resident population of 892,000 in 1989 and that 16% of the population in the UK. is 65 years or over (Central Statistical Office, 1996), table 13.3 shows the rate of hospitalisation for acute respiratory disease among different age groups. For those 65 years or older the rate of hospitalisation was 17.2 per 10,000.

Hospital case notes were available for 264 admissions. Table 13.4 shows the demographic characteristics and details of treatment received during hospitalisation for the 264 admissions. The median (range) age was 77 (16 - 99) years. More than three quarters were aged 65 years or over. More than 80% of patients received antibiotics during their

hospitalisation. Less than one third received respiratory medications whereas only about 14% received cardiovascular drugs.

Figure 13.2 shows the frequency distribution of duration of hospitalisation for 260 of the 264 admissions (data missing for four patients). The median (range) duration of hospitalisation was 7 (1 - 54) days. More than one third stayed in hospital for more than ten days and over one in ten were inpatients for three weeks or more.

Figure 13.3 shows frequency distribution of laboratory and radiological investigations for the 264 admissions. A total of 216 (81.8%) patients had at least one full blood count, 211 (79.9%) had at least one biochemistry test, and 207 (78.4%) had at least one radiological investigation. The median (range) number of blood counts, biochemistry tests, and radiological investigations were one (0 - 11), one (0 - 22), one (0 - 12) respectively.

The exact type of medications used was very wide and included almost the whole range of drugs for each body system for which they were prescribed. For the cardiovascular system the following medications were used: oral or intravenous nitrates, digoxin, anticoagulants, diuretics, and intravenous vasopressors. For the respiratory system medications used included oral or intravenous theophyllines, inhaled or nebulized adrenoceptor stimulant and antimuscarinic bronchodilators, and oral or intravenous steroids. For diabetes intravenous and subcutaneous insulin was used in addition to oral hypoglycaemics. Also a wide range of antibiotics were prescribed including ampicillin, amoxycillin, flucloxacillin, erythromycin, penicillin, cefuroxime, trimethoprim, co-amoxiclav, gentamicin, and cephradine. Table 13.5 shows the average cost of medications and investigations per admission based on a randomly selected sample of 50 admissions.

ICD-9-CM code	Diagnosis	Number (percentage)
466	Acute bronchitis and bronchiolitis	5 (1.7)
480.9	Viral pneumonia unspecified	2 (0.7)
481	Pneumococcal pneumonia	76 (25.1)
482.2	Pneumonia due to *Haemophilus influenzae*	3 (1)
482.3	Pneumonia due to *Streptococcus*	3 (1)
482.9	Bacterial pneumonia unspecified	0 (0)
485	Bronchopneumonia	101 (33.3)
486	Pneumonia organisms unspecified	39 (12.8)
487.0	Influenza with pneumonia	7 (2.3)
487.1	Influenza with other respiratory manifestations	35 (11.6)
487.8	Influenza with other manifestations	2 (0.7)
490	Bronchitis	7 (2.3)
491.0	Simple chronic bronchitis	1 (0.3)
491.2	Obstructive chronic bronchitis	5 (1.7)
491.8	Other chronic bronchitis	1 (0.3)
491.9	Unspecified chronic bronchitis	8 (2.6)
492	Emphysema	8 (2.6)

Table 13.1: **Number and percentage of patients whose primary discharge diagnosis or cause of death was influenza, pneumonia, emphysema, or bronchitis (*ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492) during the period December 1, 1989 through January 31, 1990 in Leicestershire, UK.**

Hospital	Number (percentage)
Leicester General	101 (33.3)
Glenfield General	66 (21.8)
Groby Road	44 (14.5)
Leicester Royal infirmary	38 (12.5)
Melton and District War Memorial	9 (3)
Loughborough General	9 (3)
Coalville Community	7 (2.3)
Glenfield Community	6 (2)
Rutland Memorial	5 (1.7)
Regent Hospital	5 (1.7)
Market Harborough	4 (1.3)
Fielding Palmer Cottage	3 (1)
Hinckley and District	3 (1)
Ashby and District	2 (0.6)
Catmose Vale Oakham	1 (0.3)

Table 13.2: **Number and percentage of patients whose primary discharge diagnosis or cause of death was influenza, pneumonia, emphysema, or bronchitis admitted to each of the 15 hospitals in Leicestershire, UK. during the period December 1, 1989 through January 31, 1990.**

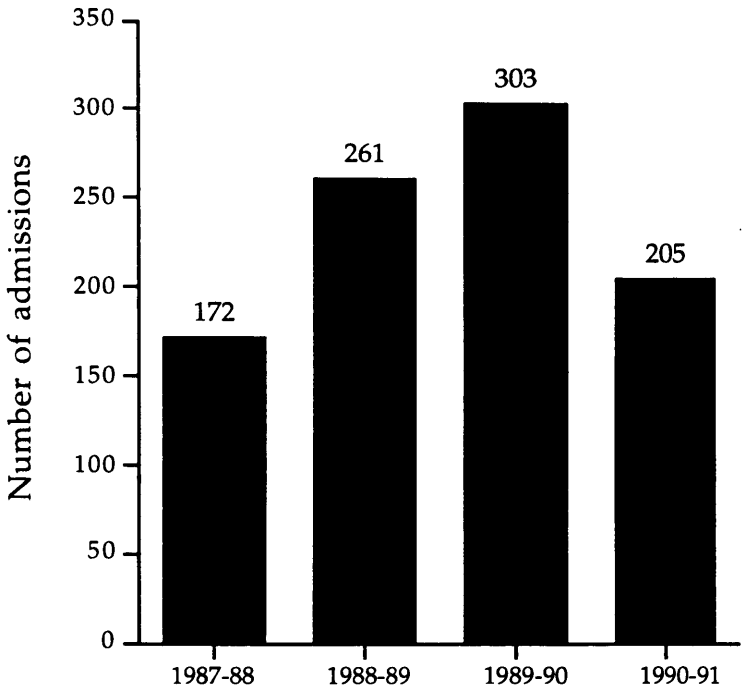

Figure 13.1: **Admissions for influenza, pneumonia, emphysema, or bronchitis (*ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492) during the period December 1, through January 31 in the years 1987 to 1991 inclusive in Leicestershire, UK.**

Age group	Number	Rate (per 10,000 persons)
16 years or over	303	3.4
16 - 43	26	0.7
44 - 64	32	1.7
65 or over	245	17.2

Table 13.3: **Rate of hospitalisation of persons with acute respiratory disease during the 1989 - 90 influenza epidemic in Leicestershire, UK.**

Characteristic	Number (percentage)
Age (years)	
16 - 43	25 (9.5)
44 - 64	30 (11.4)
65 - 74	55 (20.8)
75 - 84	81 (30.7)
85 - 94	52 (19.7)
more that 95	21 (7.9)
Sex	
Male	122 (46.2)
Female	142 (53.8)
Antibiotics during admission	
Yes	225 (85.2)
No	26 (9.8)
Missing data	13 (5)
Respiratory system medications during admission	
Yes	82 (31)
No	169 (64)
Missing data	13 (5)
Cardiovascular system medications during admission	
Yes	38 (14.4)
No	213 (80.6)
Missing data	13 (5)

Table 13.4: **Demographic characteristics and details of treatment during hospitalisation for the 264 patients admitted with influenza, pneumonia, emphysema or bronchitis during the 1989 - 90 influenza A epidemic in Leicestershire, UK.**

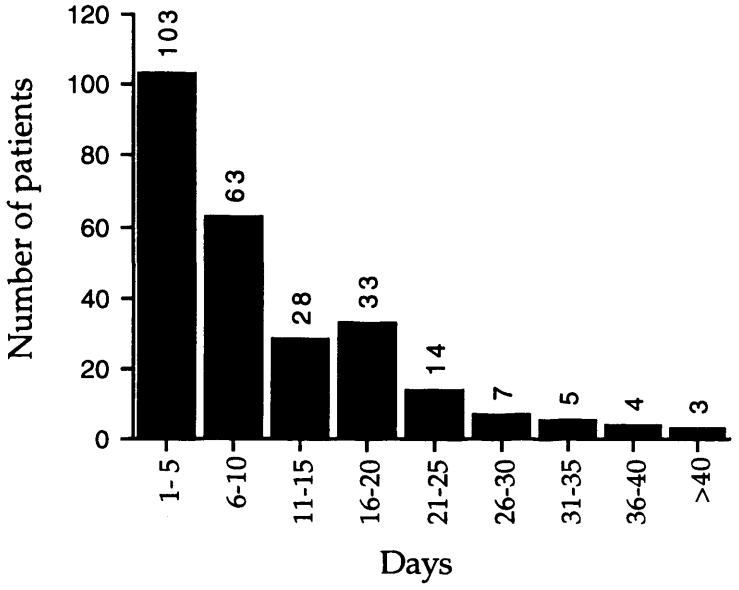

Figure 13.2: **Frequency distribution of duration of hospitalisation of admissions with acute respiratory disease to Leicestershire hospitals during the 1989 - 90 influenza A epidemic (data missing for four patients).**

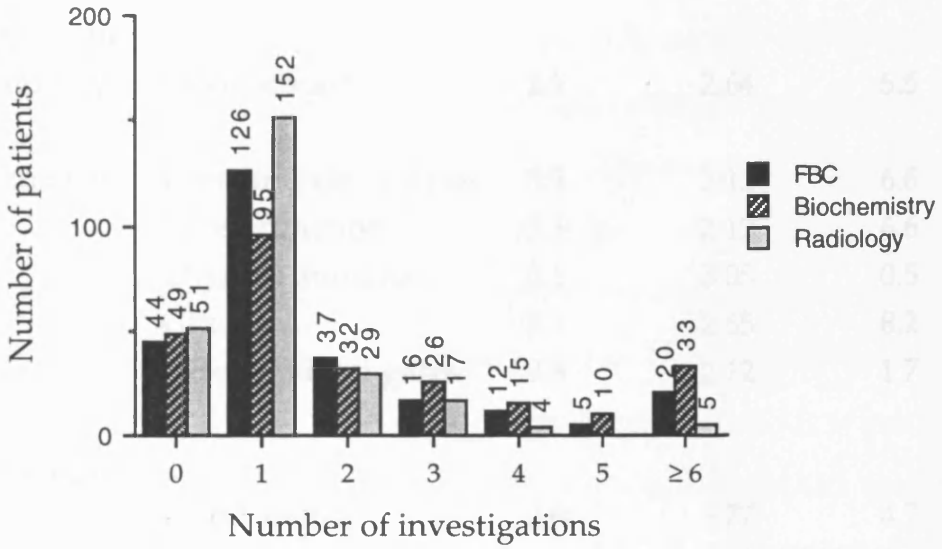

Figure 13.3: **Frequency distribution of laboratory and radiological investigations for the 264 admissions with acute respiratory diseases to Leicestershire hospitals during the 1989 - 90 influenza A epidemic (data missing on four, four, and six patients for FBC, biochemistry, and radiology respectively).**

Intervention		Mean	Cost / test in pounds	Total cost in pounds
Investigations:				
Haematology	Blood count	2.1	2.64	5.5
Biochemistry	Urea and electrolytes	3.1	2.12	6.6
	Liver function	3.1	2.12	6.6
	Thyroid function	0.1	5.05	0.5
	Glucose	3.1	2.65	8.2
	Arterial blood gases	0.8	2.12	1.7
Microbiology				
	Blood culture	0.6	7.77	4.7
	Urine culture	0.6	2.31	1.4
	Sputum culture	0.5	4.45	2.2
	Viral serology	0.2	4.99	1
Imaging and ECG				
	Chest X-ray	1.2	10.03	12
	ECG	0.3	10	3
Drugs:				
	Antibiotics			22.1
	Respiratory medications			12.5
	Cardiovascular medications			1.5
	Diabetes medications			12.7
	Analgesics			0.16
Grand total				102.36

Table 13.5: **Average cost of investigations and medications per admission based on a randomly selected sample of 50 cases.**

13.3 Discussion

During the study period in Leicestershire the number of admissions for acute respiratory illness with *ICD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492 increased by 42% in comparison with the mean number of admissions during the corresponding periods in 1987-88, 1988-89, and 1990-91 when influenza activity was less. Increased number of admissions during influenza has been noted in many surveys. These admissions result mostly from exacerbations of pre-existing chronic medical conditions. In the United States it is estimated that influenza epidemics are associated with more than 170,000 excess hospitalisations annually (Barker, 1986). However, this excess includes admissions for exacerbations of all chronic medical conditions and it would not be possible to compare it with the results of this study that focused on admissions for acute respiratory illness only.

Perrotta *et al.*, (1985) found that during the 3 influenza seasons 1978/79, 1979/80, and 1980/81, the rates of acute respiratory disease (*ICD-9-CM* codes 460 - 487) hospitalisations for adults 45 - 64 years were greater than 10 per 10,000 persons. The highest rates of hospitalisations, average 42.3 per 10,000 persons, occurred among persons aged 65 years or older. Although there is an agreement between Perrotta *et al.*, (1985) survey and this study in that the highest rates are observed in those 65 years or older, the rates observed in Perrotta *et al.*, (1985) study are much higher than the rates observed in the present study. There are three possible explanations for this difference. First, Perrotta *et al.*, (1985) included all patients with discharge diagnosis of acute respiratory illness recorded anywhere in the discharge summary, whereas the present study included only those with primary discharge diagnosis of acute respiratory illness; this is likely to have resulted in under estimation of the number of patients hospitalised for acute respiratory disease during the 1989 - 90 influenza A epidemic in

Leicestershire. A recent American study has shown that the reliability of coded diagnosis can be enhanced by including all diagnoses in discharge summaries irrespective of their sequence (Romano and Luft, 1992). Second, Perrotta *et al.*, (1985) included, in addition to patients with lower respiratory illness, those whose discharge diagnoses were upper respiratory tract illness (*CD-9-CM* codes 460 - 463), whereas no such patients were included in the present study. Third it may be possible that the different rates observed in the study by Perrotta *et al.*, (1985) and the present study are true difference because of different health care systems.

In Britain very little data is available concerning the health costs incurred during influenza epidemics in general, and there is remarkably little information on influenza as met in hospitals. Although the impact of influenza epidemics can be measured by many parameters such as general practitioner consultation rates, emergency room visits, absenteeism from work and mortality, increased number of hospitalisations probably represents the largest cost to the national health service. A total cost of £102.36 for each admission excluding 'hotel' cost represents substantial sum of money with significant impact on national health service resources. During the influenza season a 63% (95% CI 17% - 84%) (Chapter 12) reduction in admissions for acute respiratory illness with concomitant reductions in drug and inpatient investigations costs could represent considerable reduction in health costs and reduce the pressure on acute medical admissions. During the three months study period cost savings from drugs and investigations could have been at least £19,539 in Leicestershire alone.

Cost-effectiveness analysis examines the merits of reaching a desired health outcome by comparing the monetary cost of different courses of action (Freund and Dittus, 1992). For a vaccination programme, *costs* include the cost of purchasing and administering vaccine, plus the

cost of treating vaccine complications, minus the *savings* resulting from the prevention of the disease. For influenza vaccination savings include health outcomes such as reductions in mortality, morbidity, and reductions in productivity as measured, for example, by absenteeism from work. As this study dealt with only one aspect of health outcome, reduction in admissions for acute respiratory illness, it was not possible to conduct a formal cost-benefit analysis from the data collected. However, it is worth noting that the level of protection shown in this study is very comparable to that found in recently published case-control and cohort North American studies despite different health care systems (Foster *et al.*, 1992; Fedson *et al.*, 1993; Mullooly *et al.*, 1994; Nichol *et al.*, 1994). Two of these studies addressed the important issue of cost-benefit. Mullooly *et al.*, (1993) studied cost-efficacy over nine influenza seasons in North Western USA. Overall, the scheme derived a net benefit from annual vaccination programmes, but in contrast to net savings of US$6.11 per vaccination for high-risk patients, there was a net cost of US$4.82 per vaccination for non-high-risk individuals. However, the admission rates were approximately seven-fold higher for high-risk patients than for non-high-risk elderly. On the other hand Nichol *et al.*, (1994) showed that over a period of three years vaccination of people 65 years of age or older resulted in overall cost savings of US$117 per person vaccinated. Overall 13% of study subjects had coronary heart disease, 9% had diabetes mellitus and 8% had chronic lung disease. Given the fact that patients in this study were hospitalised for a median period of 7 days, that 72.4% of the admissions had 'high-risk' conditions for which influenza vaccine is recommended by the DoH (Table 12.1), that the costs incurred during hospitalisation as a result of investigations and treatment was £102.36 for each admission, and that influenza vaccines are not expensive and cost about five pounds per dose (British Medical Association and Royal Pharmaceutical Society of Great

Britain, 1996), it is conceivable that vaccination is also cost-effective in this setting. However, in the absence of a formal cost-benefit analysis this can not be confirmed and clearly there is a need for such an assessment in the UK.

CONCLUSION

Conclusion

Introduction

Influenza epidemics impose an enormous burden in terms of morbidity including hospital admissions, mortality, economic and social costs. The 1989 - 90 influenza epidemic was the worst to have hit the United Kingdom since 1976 causing 29,000 deaths. In spite of annual recommendations from the DoH the level of immunisation among high-risk patients remains very low. Data on the effectiveness of vaccine among the elderly was scanty and of poor quality. In order to support vaccination more information was required from a well designed study. Because influenza vaccines are licensed and recommended by the Department of Health it is deemed unethical to mount prospective double-blind placebo-controlled studies to test their efficacy. Case-control studies are an alternative method of assessing vaccine effectiveness. Therefore the effectiveness of influenza vaccine was assessed by two case-control studies. They focused on vaccine effectiveness in preventing deaths (the mortality study) and hospitalisation (the hospital admission study) as primary endpoints, but other endpoints were identified and presented.

General conclusions

Although ethical approval was obtained from all 36 local research ethics committees involved, review of the practices of local research ethics committees revealed much diversity and considerable variation in the issues raised. None of these committees were found to conform exactly to Royal College of Physicians guidelines. Obtaining ethical approval for this multi-centre study proved to be time consuming and expensive; the time to obtain ethical approval varied between 6 to 208 days and one third of

the committees did not approve the project within 3 months. These findings support the recommendation for a central or regional review body of multi-centre studies which would be acceptable to all local research ethics committees.

The effectiveness of influenza vaccine in preventing deaths was found to be 41% (95% CI 13 - 60%). Vaccine effectiveness was found to be greater after repeated annual vaccination than after first time administration: among subjects who received the vaccine for the first time in 1989, vaccination reduced mortality by only 9% (95% CI 0 - 50); whereas among those who had also been vaccinated previously, mortality was reduced by 75% (95% CI 31 - 91). Vaccination was equally effective in subjects who lived in institutions and in the community, and in subjects with high-risk medical conditions and those without.

Among all cases and controls (1092 individuals) influenza vaccine up-take was only 21.5% during the 1989 - 90 epidemic, but 840 (76.9%) of the 1092 individuals had an indication for vaccination as recommended by the DoH. There was no significant difference in the proportion of patients with 'high-risk' chronic medical conditions who were vaccinated (x^2 =7, p = 0.07) indicating that no 'high-risk' group was specifically targeted. Clearly that there are serious deficiencies in vaccine delivery to 'high-risk' individuals. However, the overall vaccination rate was higher in 'high-risk' groups (228 of 840, 27.1%) as compared with those without an indication for vaccination (7 of 252, 2.7%) (x^2 = 49.7, D.F. = 1, $p < 0.05$) indicating a high degree of targeting. Multiple logistic regression showed that three factors significantly affected the likelihood of immunisation in 1989 - 90: more frequent consultations with GP during the 12 months before death (OR 1.04, CI 1.03 - 1.04), living in residential care (OR, 1.45, CI 1.17 - 1.79), and 'previous' vaccination (between 1985 - 88) (OR 7.61, CI 6.06 - 9.56).

Of the 315 fatal influenza cases identified in 36 District Health Authorities, 299 (94.9%) were 65 years or older and 263 (83.5%) had a condition regarded as an indication for vaccination by the DoH. Clearly the great majority of deaths occurred in those 65 years or over with chronic ill-health. These observations do not provide a strong argument to extend the current immunisation policy to include all individuals 65 years or over irrespective of chronic ill-health as the impact on certified influenza death would be relatively small.

Drugs were prescribed during the final illness for at least 233 (74%) cases. Details on duration of final illness were available for 275. Of these 46 (17%) died within the first 48 hours after onset of final illness and (64%) died within the first seven days. The rapid deterioration following onset of final illness emphasises the importance of preventing infection rather than trying to treat it with antibiotics or antiviral agents.

In Leicestershire during the influenza epidemic of 1989 - 90, the number of patients admitted with acute respiratory disease (*CD-9-CM* codes 466, 480.9 through 482.9, and 485 through 492) increased by 42% during the epidemic period when compared with the mean number of admissions during the corresponding periods in the two seasons before and the season after the epidemic when influenza activity was lower (303 *versus* 212). Hospitalisation rate for acute lower respiratory tract illness was highest for those 65 years or over (17.2 per 10,000 individuals). Analysis of 156 admissions and 289 controls showed that influenza vaccine reduced the number of hospital admissions by 63% (95% CI 17 - 84%). Vaccine was equally effective when used in subjects with 'high-risk' medical conditions and those without (P = 0.23), or when used in subjects living in residential care and those living in their own homes (P = 0.88). However, there was a marked trend towards enhanced vaccine effectiveness among subjects living in residential care

(V_E 70%; 95% CI 32 - 87%) compared with those living in their own homes (V_E 19; 95% CI 0 - 82%).

Individuals admitted with acute respiratory illness during the 1989 - 90 influenza epidemic to Leicestershire hospitals were mostly elderly: median age was 77 years and more than three quarters were aged 65 years or over. The great majority, more than 80%, were prescribed antibiotics during hospitalisation, respiratory medications were prescribed for 31%, and cardiovascular medications for 14%. More than 80% were admitted to teaching hospitals and the median duration of hospitalisation was seven days. More than one third stayed in hospital for more than ten days and over one in ten were inpatients for three weeks or more. A total of 216 (81.8%) patients had at least one full blood count, 211 (79.9%) had at least one biochemistry test, and 207 (78.4%) had at least one radiological investigation. The average cost of investigations carried out and treatment given was estimated at £102.36 per admission; this excludes 'hotel' costs. Given that influenza vaccine is not expensive and costs about £5 it is conceivable that vaccination is cost-effective in people with 'high-risk' conditions specially if we were to take into consideration consultations in the community and their associated costs. However, in the absence of a formal cost-benefit analysis this can not be confirmed.

Sir Austin Bradford Hill (Hill, 1984) maintained that the 'truth' of an epidemiological association could be supported by such factors as the strength of the measured association and the consistency with which the association is demonstrated in different studies by different investigators. The level of influenza vaccine effectiveness in reducing mortality in this study (V_E 41%; 95% CI 13 - 60%) is comparable to those observed in two recently published case-control and cohort North American studies and one cohort British study. Fedson *et al.*, (1993) compared the health and influenza immunisation status of over 5000 non-institutionalised people

aged 45 years and over who were admitted to hospitals for lower respiratory tract conditions during two epidemics, with matched controls. Influenza vaccine prevented 43 - 65% of hospital deaths from respiratory conditions, and 27 - 30% of hospital death from all causes. Nichol *et al.*, (1994) conducted a large cohort study in elderly non-institutionalised individuals over three seasons, 1990 - 91 to 1992 - 93, inclusive. Vaccine was 39 - 54% effective in reducing mortality from all causes. Fleming *et al.*, (1995) reported a large cohort study using computerised general practitioners' records on about 10,000 patients aged 55 years or older in Birmingham, UK. These investigators found that recent influenza immunisation afforded a 75% (95% CI 21 - 92%) protection against death from all causes.

Similarly the level of vaccine effectiveness in reducing hospitalisation for acute respiratory disease observed in this study (V_E 63%; CI 17 - 84%) accord with that shown in four carefully designed North American studies. Fedson *et al.*, (1993) found that influenza vaccine prevented 32 - 39% of hospital admissions for influenza and pneumonia, and 15 - 34% of admissions for all respiratory conditions. Foster *et al.*, (1992) reported a case-control study among 449 non-institutionalised admissions for pneumonia and influenza aged 65 years or over and 1458 matched controls. Immunisation was associated with a 45% reduction in admissions for pneumonia and influenza. Mullooly *et al.*, (1994) studied vaccine effectiveness over nine influenza seasons, 1980 - 81 to 1988 - 89. Vaccine was 30% effective in preventing influenza and pneumonia hospitalisation over the nine years, but significant protection of 83, 70 and 51% was noted only in 1980/81, 1982/83 and 1986/87 respectively. Nichol *et al.*, (1994) showed that vaccine was 48 - 57% effective in reducing hospitalisation for pneumonia and

influenza, and 27 - 39% effective in reducing admissions for all acute and chronic respiratory conditions.

The remarkable consistency of evidence among these studies suggest that influenza vaccine is indeed effective in reducing influenza mortality and hospitalisation for acute respiratory disease and should be given to all individuals who are likely to develop these complications as specified in the DoH guidelines.

APPENDIXES

APPENDIX I

Letter to chairmen of local research ethics committees

Dear Dr

Influenza Deaths 1989 - 1990 and the efficacy of Influenza Vaccine

You may recall that the influenza outbreak in 1989 - 1990 was the worst to have hit England and Wales since 1976, and was responsible, either directly or indirectly for about 26000 deaths. The Chief Medical Officer and his Influenza Advisory Committee were extremely concerned about the deaths and the low level of immunisation, and the CMO`S annual recommendations on influenza vaccine have since been strengthened.

General practitioners and patients have voiced concern about the efficacy of influenza vaccine among the elderly, but because influenza vaccines are licensed and recommended by the Department of Health it is deemed unethical to mount prospective double blind placebo - controlled studies to test their efficacy. Alternative strategies are being considered by the MRC and PHLS (such as case control studies), but because influenza epidemics are sporadic in nature the Department of Health wishes to extend the pilot study carried out in Leicestershire during 1989 - 1990 (see enclosure). Accordingly we have contacted the Director of Public Health Medicine in your Health Authority, and through him / her we have identified patients who died during the period week 44, 1989 to week 8 1990 with influenza anywhere on the death certificate (i.e. 1a, b, or c, and 2). Having identified the patients, we would like to seek ethical committee approval to: review the patients' notes held by the FSHA to obtain details of these fatal cases (see detailed Questionnaire) and identify controls matched for age, sex, residence and chronic ill health from GP records, and study their GP notes. The efficacy of immunisation in preventing fatal influenza will then be estimated.

We have been granted ethical approval from Leicestershire Health Authority (see copy), and are unsure whether we will need local ethical approval as well. If this is the case I would be grateful if you could send me copy of your Ethical Committee submission form.

Yours sincerely

Dr. A. H. Ahmed,
Clinical Research Fellow

APPENDIX II

Letter to Directors of Public Health

Dear Dr.

Influenza Deaths 1989 - 1990 and the efficacy of Influenza Vaccine

You will recall that the influenza outbreak in 1989 - 1990 was the worst to have hit England and Wales since 1976, and was responsible, either directly or indirectly for about 26000 deaths. The Chief Medical Officer and his Influenza Advisory Committee (of which I am a member) were extremely concerned about the deaths and the low level of immunisation, and the CMO'S annual recommendations on influenza vaccine have since been strengthened. General practitioners and patients have voiced concern about the efficacy of influenza vaccine among the elderly, but because influenza vaccines are licensed and recommended by the Department of Health it is deemed unethical to mount prospective double blind placebo - controlled studies to test their efficacy. Alternative strategies are being considered by the MRC and PHLS (such as case control studies), but because influenza epidemics are sporadic in nature the Department of Health wishes to extend the pilot study carried out in Leicestershire during 1989 - 1990 (see enclosure). Accordingly I am contacting Directors of Public Health Medicine.

My reason for writing is to seek your assistance in identifying patients in your Health Authority who died during the period week 44, 1989 to week 8 1990 with influenza anywhere on the death certificate (i.e. 1a, b, or c, and 2). Clearly I would not expect you to identify the patients for us - rather I hope that one of my team could review the Register for the period to identify the individual patients, (their name, age, or date of birth, address at time of death and the certified cause(s) of death.) Having identified the patients (or the ability to identify them), we would seek local ethical committee approval to review the patients' notes held by the FHSA.

I appreciate that this may appear to be yet another tiresome task, but your help would be very much appreciated. I look forward to hearing from you in the near future indicating whether or not it would be possible to identify deceased patients in your Health Authority.

With kind regards.
Yours sincerely

K. G. Nicholson MD, FRCP, MRCPath
Senior Lecturer in Infectious Diseases

APPENDIX III

District Health Authorities involved

1. North Derbyshire
2. Southern Derbyshire
3. North Nottinghamshire
4. Leicestershire,
5. Nottingham
6. Rotherham
7. Bolton
8. North Manchester
9. Blackpool Wyre & Fylde
10. Blackburn Hyndburn & Ribble Valley
11. Bury
12. Lancaster
13. Preston
14. North Warwickshire
15. Wolverhampton
16. Macclesfield
17. Leeds
18. South Warwickshire
19. Liverpool
20. Salford
21. Tameside & Glossop
22. Trafford
23. North Worcestershire
24. Herefordshire
25. Mid-Staffordshire
26. South East Staffordshire
27. North Staffordshire
28. Sandwell
29. Solihull
30. West Birmingham
31. North Birmingham
32. Walsall
33. Halton
34. Bradford
35. Central Manchester
36. Wakefield

APPENDIX IV

Letter to FHSA General Managers

Dear Mr.

Influenza Deaths 1989 - 1990 and the efficacy of Influenza Vaccine

You may recall that the influenza outbreak in 1989 - 1990 was the worst to have hit England and Wales since 1976, and was responsible, either directly or indirectly for about 26000 deaths. The Chief Medical Officer and his Influenza Advisory Committee (of which I am a member) were extremely concerned about the deaths and the low level of immunisation, and the CMO`S annual recommendations on influenza vaccine have since been strengthened.

General practitioners and patients have voiced concern about the efficacy of influenza vaccine among the elderly, but because influenza vaccines are licensed and recommended by the Department of Health it is deemed unethical to mount prospective double blind placebo-controlled studies to test their efficacy. Alternative strategies are being considered by the MRC and PHLS (such as case control studies), but because influenza epidemics are sporadic in nature the Department of Health wishes to extend the pilot study carried out in Leicestershire during 1989 - 1990 (see enclosure).

Accordingly I contacted Directors of Public Health Medicine and through them identified patients who died during the period week 44, 1989 to week 8 1990 with influenza anywhere in the death certificate (i.e. 1a, b or c and 2). Included is the list of patients in your Health Authority which includes: registration district and sub-district, name, date of birth, date and place of death and usual address.

In order to be able to review the notes of these patients, we have obtained ethical approval from both Leicestershire Ethical Committee as well as from ..... research Ethics Committee (see enclosure).

My reason for writing is to seek your assistance in reviewing the case notes of these patients held by the FHSA, and extract details about their age, sex, previous health, etc. (see detailed questionnaire). Clearly I would not expect you to do this for us - rather I hope, that if these notes could be located, that one of my team could be allowed to review the case notes and extract the details during a visit to your premises.

I appreciate that this may appear to be yet another tiresome task, but your help would be very much appreciated. I look forward to hearing from you in the near future indicating whether or not it would be possible to locate the case notes of these patients.

With kind regards.
Yours sincerely

K. G. Nicholson MD, FRCP, MRCPath
Senior Lecturer in Infectious Diseases

APPENDIX V

Influenza Deaths 1989 - 1990 and the Effectiveness of Influenza Vaccine (cases)

Name : .....

Sex : Male [ ] Female [ ]

Date of birth : ...../...../.....

Date of death : ...../...../..... Age at time of death : .....Years

Address : .....
.....

Place of Residence:

Nursing home [ ]

Residential care home [ ]

Part III accommodation [ ]

Hospital [ ]

Private residence [ ]

Warden assisted flat [ ]

Health Authority: .....

G.P. address: .....
.....

Pre-existing chronic disease:

Cardiovascular	[ ]	Pulmonary	[ ]
Diabetes	[ ]	Endocrine	[ ]
Renal	[ ]	Neurological	[ ]
Malignancy	[ ]	Auto immune	[ ]
Others	[ ]		

Pre-existing chronic disease - Clinical details : .....
.....
.....
.....
.....
.....
.....

Regular medications for chronic disease:

Name	Dose	Duration	Frequency	Route	indication
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
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.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....

Number of GP consultations during previous 12 month (excluding consultations relating to final illness) : .....

Admissions to hospital during past 5 years Please provide details : .....
.....
.....
.....
.....
.....
.....
.....
.....

Final illness :

Seen by GP Yes [ ] Number [ ] No [ ]

Date of onset of final illness : ...../...../.....

Total duration of final illness : ..... Days

New drugs prescribed by GP during final illness :

Name	dose	Duration	Frequency	Route
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....

Was patient admitted to hospital during final illness Yes [ ] No [ ]

Date of admission : ...../...../.....

Hospital if known :

.....

.....

Influenza vaccine history:

Year	Vaccinated			Date of vaccination
1989 / 1990	No	Refused	Yes	.....
1988 / 1989	No	Refused	Yes	.....
1987 / 1988	No	Refused	Yes	.....
1986 / 1987	No	Refused	Yes	.....
1985 / 1986	No	Refused	Yes	.....

Pneumococcal vaccination: No [ ] Yes [ ] Date: .....

Details from death certificate:

Entry Number : .....

Registration district : .....

Sub district : .....

Cause of Death:

1a - .....

1b - .....

1c - .....

II - .....

APPENDIX VI

Influenza Death 1989 - 1990 and the Effectiveness of Influenza Vaccine (controls)

Name : .....

Sex : Male [ ] Female [ ]

Date of birth : ...../...../.....

Date of death : ...../...../..... Age at time of death : .....Years

Address : .....

.....

Same address at time of the epidemic Yes [ ] No [ ]

Place of Residence

Nursing home [ ]

Residential care home [ ]

Part III accommodation [ ]

Hospital [ ]

Private residence [ ]

Warden assisted flat [ ]

Health Authority : .....

GP Practice address :

.....

.....

Pre-existing chronic disease:

Cardiovascular	[ ]	Pulmonary	[ ]
Diabetes	[ ]	Endocrine	[ ]
Renal	[ ]	Neurological	[ ]
Malignancy	[ ]	Auto immune	[ ]
Others	[ ]		

Pre-existing chronic disease - Clinical details : .....
.....
.....
.....
.....
.....
.....

Regular medications (for chronic disease) :

Name	Dose	Duration	Frequency	Route	indication
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
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.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....

Number of GP consultations during previous 12 month (excluding consultations relating to final illness) : .....

Admissions to hospital during past 5 years Please provide details : .....
.....
.....
.....
.....
.....
.....
.....
.....
.....

Final illness :

Seen by GP Yes [ ] Number [ ] No [ ]

Date of onset of final illness : ...../...../.....

Total duration of final illness : ..... Days

New drugs prescribed by GP during final illness :

Name	dose	Duration	Frequency	Route
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....

Was patient admitted to hospital during final illness Yes [ ] No [ ]

Date of admission : ...../...../.....

Hospital if known : .....

Influenza vaccine history :

Year	Vaccinated			Date of vaccination
1990 / 1991	No	Refused	Yes	
1989 / 1990	No	Refused	Yes	.....
1988 / 1989	No	Refused	Yes	.....
1987 / 1988	No	Refused	Yes	.....
1986 / 1987	No	Refused	Yes	.....
1985 / 1986	No	Refused	Yes	.....

Pneumococcal vaccination No [ ] Yes [ ] Date

Details from death certificate :

Entry Number : .....

Registration district : .....

Sub district : .....

Cause of Death :

1a - .....

1b - .....

1c - .....

II - .....

APPENDIX VII

Influenza Vaccine Admission Study (cases)

Demographic data:

Hospital Number: .....

Name:.....

Sex: Male [ ] Female [ ]

Date of birth: ...../...../..... Age at the time of admission: .....

Occupation:
.....

History of smoking: Yes [ ] No [ ] No information [ ]

Current smoker: Yes [ ] No [ ] No information [ ]

Number currently smoked /day:
.....

Address:
.....
.....
.....
.....

Type of residence:

Nursing home [ ]

Residential care home [ ]

Part III accommodation [ ]

Hospital [ ]

Private residence [ ]

Warden assisted flat [ ]

General Practitioner:

.....
.....
.....
.....
.....

Regular medications at the time of admission:

.....
.....
.....
.....
.....
.....
.....

Number of drugs: [ ]

Which systems were involved:

Cardiac	(1)
Respiratory	(2)
Neurological	(3)
Renal	(4)
Malignancy	(5)
Diabetic	(6)
Endocrine (other)	(7)
Autoimmune	(8)
Other	(9)

Other details [.....]

Total number of systems involved: [ ]

Length in years of chronic medical illneess:

No information	[ ]
0 - 4	[ ]
5 - 9	[ ]
10 - 15	[ ]
16 - 20	[ ]
21 - 25	[ ]
> 26	[ ]

Previous health status:

General good health [ ]
Chronically ill stable [ ]
Chronically ill deteriorating [ ]

Number of previous hospital amissions in last 5 years: [ ]

Influenza vaccine history :

Year	Vaccinated			Date of vaccination
1989 / 1990	No	Refused	Yes	.....
1988 / 1989	No	Refused	Yes	.....
1987 / 1988	No	Refused	Yes	.....
1986 / 1987	No	Refused	Yes	.....
1985 / 1986	No	Refused	Yes	.....

Details of illness requiring hospital admission:

Date of admission: ...../...../...../

Duration of hospital stay in days: .....

Hospital: ..... Code: .....

Consultant: ..... Code: .....

Date of discharge: ...../...../.....

ICD classification ascribed to illness: .....

Presenting features of illness:

General symtoms:	Yes [1]	No [2]
Confusion	[ ]	
Malaise	[ ]	
Headache	[ ]	
Myalgia	[ ]	
Rigors/Chills/Shivers	[ ]	
Anorexia	[ ]	
Nausea/vomiting	[ ]	
Drowsiness	[ ]	

Respiratory Symptoms:

Coryzal Symptoms	[ ]
Sore Throat	[ ]
Non Productive Cough	[ ]
Productive Cough (Non Purulent Sputum)	[ ]
Productive Cough (Purulent sputum)	[ ]
Haemoptysis	[ ]
Chest Pain	[ ]
Dyspnoea	[ ]

Other Symptoms List:

.....

.....

.....

.....

.....

.....

.....

Clinical findings on examination:

Weight: ..... kg Temp ..... ^{0}C

Level of conciousness according to Glasgow coma scale: .....

Heart rate / minute: ..... BP: ..... mm/Hg

Arryhthmia: [ ] Yes [1] No [2]

State type: .....

Respiratory examination:

Respiratory rate / min: .....

Presence of cyanosis	[ ]
Reduced expansion	[ ]
Dullness to percussion	[ ]
Normal breath sounds	[ ]
Pleural rub	[ ]
Crackles	[ ]
Bronchial Breathing	[ ]

Other findings:

.....

.....

.....

.....

.....

.....

Drugs used to treat illness requiring admission

Name of drug	Dose	No. of doses over 24 hours	No. of days on drug

Investigations:

No. of FBCs in the notes [ ]
No. of Biochemistry tests in the notes [ ]
No. of Radiological investigations in the notes [ ]
No. of Blood cultures in the notes [ ]
No. of sputum cultures in the notes [ ]
No. of Urine cultures in the notes [ ]
No. of Drug assays in the notes [ ]

Other investigations

Name of test Number

Results of investigations

Admission Full Blood Count:

Haemoglobin	[ ]		
White cell count	[ ]	% Polymorphs	[ ]

Biochemistry:

Sodium	[ ]	ALT	[ ]
Potassium	[ ]	Bilirubin	[ ]
Urea	[ ]	Gama GT	[ ]
Creatinine	[ ]	Alk Phos	[ ]
Total protein	[ ]	Albumin	[ ]

Blood Gases:

PaO_2 pH

$PaCO_2$

Chest X-Ray:

	Yes	No
Performed	[ ]	[ ]
Unilateral infiltrtion	[ ]	[ ]
Bilateral infiltration	[ ]	[ ]
Pleural effusions	[ ]	[ ]
Lung fields clear	[ ]	[ ]

Other abnormalities state below:

Sputum:

Sent for culture Yes [ ] No [ ]

Result

No organism	[ ]
Strept pneumonia	[ ]
Staph pneumonia	[ ]
E coli	[ ]
Haemophilus influenza	[ ]
Mixed flora	[ ]
Others	[ ]

Blood culture:

Sent for culture Yes [ ] No [ ]

Result ..... Organism

.....

Serology:

Acute	Date	*Convalescent*	Date .....
Date of collection		Date of collection	
Lab No. [ ]		Lab No. [ ]	
Influeza A	[ ]		[ ]
Influenza B	[ ]		[ ]
RSV	[ ]		[ ]
Adenoviruses	[ ]		[ ]
Mycoplasma	[ ]		[ ]
Clamydia	[ ]		[ ]

Other viruses isolated:

Complications:

	Yes	No
Death within 24 hours of admission (fulminating disease)	[ ]	[ ]
Lung abscess	[ ]	[ ]
Pleural effusion	[ ]	[ ]
Empyema	[ ]	[ ]
Septic emboli	[ ]	[ ]
Neurological complications	[ ]	[ ]
Otitis	[ ]	[ ]
Sinusitis	[ ]	[ ]
Myocardial infarction	[ ]	[ ]
Arrhythmia	[ ]	[ ]
Cardiac failure	[ ]	[ ]
	[ ]	[ ]

Other complications:

Transfer to another ward or department eg ITU/CCU Yes No

Details

Date of discharge ...../...../.....

Total number of days in hospital .....

Died Yes No

Certified cause of death:

1a .....

1b .....

1c .....

2 .....

Discharge to usual place of residence Yes No

Other:

Nursing home .....

Part III .....

Other hospital .....

Private residence .....

Warden aided .....

PM findings

Clinic visit

Date Outcome

APPENDIX IIX

Letter to general practitioners

Dear Dr

Hospital admissions for influenza pneumonia and bronchitis during the 1989 - 1990 influenza epidemic and the efficacy of influenza vaccine

We are co-ordinating a Department of Health research project to assess the efficacy of influenza vaccination in reducing admissions for influenza, pneumonia and bronchitis, collating data from the 1989-1990 epidemic which was the worst to have hit England and Wales since 1976

All patients admitted to Leicestershire hospitals with the diagnosis of 'influenza' 'pneumonia', or 'bronchitis' during the 1989-1990 winter were identified and their hospital case notes were reviewed. We would now like to know their vaccination status, and I am writing to seek your assistance.

Please find enclosed a list of patients who were admitted from your practice. I would be extremely grateful if you could complete the enclosed questionnaire indicating their influenza vaccination status over 5 years prior to admission. I appreciate that this is yet another tiresome task but your help with this matter is very much appreciated. Ethical approval for this project has been obtained and if you feel that would prefer some one from my Department to review the case notes this could be arranged.

Yours sincerely

Dr. K G Nicholson MD, FRCP, FRCPath
Senior Lecturer in Infectious Diseases

Hospital admissions for influenza pneumonia and bronchitis during the 1989-1990 influenza epidemic and the efficacy of influenza vaccine

Name:.....

Date of birth: .....

Influenza vaccine history :

Year	Vaccinated	Date of vaccination
1989 / 1990	No Refused Yes	.....
1988 / 1989	No Refused Yes	.....
1987 / 1988	No Refused Yes	.....
1986 / 1987	No Refused Yes	.....
1985 / 1986	No Refused Yes	.....

Date: ...../...../.....

Practice: .....

.....

.....

Signature: .....

APPENDIX IX

Influenza Vaccine Admission Study (controls)

Name : .....

Sex : Male [ ] Female [ ]

Date of birth : .....

Date of death : ...../...../.....Age at time of admission : .....Years

Address :

.....

.....

.....

Same area at time of the epidemic Yes [ ] No [ ]

Occupation: .....

History of smoking: Yes [ ] No [ ]

Type of Residence:

Nursing home [ ]

Residential care home [ ]

Part III accommodation [ ]

Hospital [ ]

Private residence [ ]

Warden assisted flat [ ]

GP Practice address :

.....
.....
.....
.....
.....

Pre-existing chronic disease up to 1990:

Cardiovascular	[ ]	Pulmonary	[ ]
Diabetes	[ ]	Endocrine	[ ]
Renal	[ ]	Neurological	[ ]
Malignancy	[ ]	Auto immune	[ ]
Others	[ ]		

Total number of systems involved [}

Length in years of chronic medical illness

No information	[ ]
0 - 4	[ ]
5 - 9	[ ]
10 - 15	[ ]
16 - 20	[ ]
21 - 25	[ ]
> 26	[ ]

Previous Health Status:

General good Health	[ ]
Chronically ill stable	[ ]
Chronically ill deteriorating	[ ]

Number of Hospital Admissions in the last 5 years (Prior to 1990): [ ]

Regular medications (for chronic disease) up to 1990 :

Name	Dose	Duration	Frequency	Route	indication
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
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.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....

Number of Drugs [ ]

Record of influenza-like illness or chest infection during winter 1989-1990

Yes [ ] No [ ]

CXR during winter 1989-1990: Yes [ ] No [ ]

Influenza vaccine history :

Year	Vaccinated	Date of vaccination
1989 / 1990	No Refused Yes	.....
1988 / 1989	No Refused Yes	.....
1987 / 1988	No Refused Yes	.....
1986 / 1987	No Refused Yes	.....
1985 / 1986	No Refused Yes	.....

Details from death certificate :

Cause of Death :

1a - .....

1b - .....

1c - .....

II - .....

P M Yes [ ] No [ ]

If yes findings:

.....

.....

.....

.....

.....

REFERENCES

References

Air GM, Laver WG, Webster RG. Mechanism of antigenic variation in an individual epitope on influenza virus N9 neuraminidase. *J Virol* 1990;**64:**2797-803.

Albazzaz MK, Harvey JE, Grilli EA, Caul EO, Roome AP. Subunit influenza vaccination in adults with asthma: effect on clinical state, airway reactivity, and antibody response. *Br Med J* 1987;**294**:1196-7.

Alford RH, Kasel JA, Gerone PJ, Knight V. Human influenza resulting from aerosal inhalation (31255) *Proc Soc Exp Biol Med* 1966;**122**:800-804.

Anand SC, Itkin IH, Kind LS. Effect of influenza vaccine on methacholine (Mecholyl) sensitivity on patients with asthma of known and unknown origin. *J Allergy* 1968;**42**:187-92.

Arden NH, Patriarca PA, Kendal AP. Experiences in the use and efficacy of inactivated infuenza vaccine in nursing homes, in Kendal AP, Patriarca PA (eds): Options for the control of influenza. New York, Alan R Liss In, 1986, pp 155-68.

Ashley J, Smith T, Dunnel K. Deaths in Great Britain associated with the influenza epidemic of 1989/90. Population Trends. 1991;**65:**16-20.

Bamford CR, Sibley WA, Laguna JF. Swine influenza vaccination in patients with multiple sclerosis. *Arch Neurol* 1978;**35:**242-3.

Banks J, Bevan C, Fennerly A, Ebden P, Walters EH, Smith AP. Association between rise in antibodies and increase in airway senstivity after intramuscular injection of killed influenza virus in asthmatic patients. *Eur J Respir Dis* 1985;**66:**268-722.

Barker W, Raubertas R, Menegus M, O'Brien D, Freundlich C, Betts R. Case-control study of influenza vaccine effectiveness in preventing pneumonia hospitalization among older persons, Monroe County, New York, 1898-1992. *Options for control of influenza II.* Edited by

Hannoun C, Kendal AP, Klenk HD, Ruben FL. Amsterdam: Elsevier; 1993:143-51.

Barker WH, Mullooly JP. Influenza vaccination of elderly persons. Reduction in pneumonia and influenza hospitalisation and deaths. *JAMA* 1980;**244**:2547-9.

Barker WH, Mullooly JP. Pneumonia and influenza deaths during epidemics: implication for prevention. *Arch Intern Med* 1982;142:85-89.

Barker WH. Excess pneumonia and influenza associated hospitalisation during influenza epidemics in the United States, 1970 - 78. *Am J Public Health* 1986;**76**:761-5.

Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TVO, Tobias M. Viral respiratory tract infection and exacerbation of asthma in adult patients. *Thorax* 1988;**43**:697-83.

Bell JA, Ward TJ, Kapikian AZ, Shelokov A, Reichelderfer TE, Huebner RJ. Artificially induced Asian influenza in vaccinated and unvaccinated volunteers. *JAMA* 1957;**165**:1366-73.

Bell TD, Chai H, Berlow B, Danials G. Immunization with killed influenza vaccine in children with chronic asthma. *Chest* 1978;**73**:140-5.

Bell TD, Leffert F, McIntosh K. Monovalent influenza A/New Jersey/76 virus vaccines in asthmatic children: pulmonary function and skin tests for allergy. *J Infect Dis* 1977;**136 (suppl)**:S612-5.

Belshe RB, Burk B, Newman F, Cerruti RL, Sim IS. Resistance of influenza A virus to amantadine and rimantadine: one decade of surveilance. *J Infect Dis* 1989;**159(3)**:430-5.

Beyer W EP, Palache AM, Baljet M, Masurel N. Antibody induction by influenza vaccines in the elderly: a review of the literature. *Vaccine* 1989;**7**:385-93.

Bouter KP, Diepersloot RJA, Van Romunde LKJ, Uitslager R, Masurel N, Hoekstra JBL, Erkelens DW. Effect of epidemic influenza on

ketoacidosis, pneumonia and death in diabetes mellitus: a hospital register survey of 1976 - 1979 in the Netherlands. *Diabetes Research and Clinical Practice*. 1991;**12**:61-8.

Breslow NE, Day NE, (1980). Statistical methods in cancer research, vol 1. The analysis of case-control studies, Lyon: International Agency for Research on Cancer.

Briggs JD, Timbury MC, Paton AM, Bell PRF. Viral infection and renal transplant rejection. *Br Med J* 1972;**4**:520-22.

Briggs WA, Rozek RJ, Migdal SD, Shillis JL, Brakett RG, Brandon FB, Mahajan SK, McDonald FD. Influenza vaccination in kidney transplant recipients: cellular and humoral immune responses. *Ann Intern Med* 1980;**92:**471-77.

British Medical Association and Royal Pharmaceutical Society of Great Britain, 1996. British National Formulary No 31. London: The Pharmaceutical Press, 1996.

Brodman R, Gilfillan R, Glass D, Schur PH. Influenza vaccine response in systemic lupus erythematosus. *Ann Inter Med* 1978;**88:**745-40.

Bryson YJ, Monahan C, Pollack M, Sheilds WD. A prospective double-blind study of side-effects associated with the administration of amantadine for influenza A prophylaxis. *J Inf Dis* 1980;**141:**543-7.

Buckman CA, Doyle WJ, Skoner DP, Post JC, Alper CM, Seroky JT, Anderson K, Preston RA, Hayden FG, Fireman P, Elrlich GD. Influenza A virus-induced acute otitis media. *J Inf Dis* 1995;**172**:1348-51.

Burnet FM, Influenza virus on the developing egg. 1. Changes associated with the development of an egg-passage strain of virus. *Br J Exp Path* 1936;**17**:282-9.

Burns A, Jacoby R, Luthert P, Levy R. Cause of death in Alzheimer's disease. *Age and ageing*, 1990;**19**:341-4

Campbell BG, Edwards RL. Safety of influenza vaccination in adults with asthma. *Med J Aust* 1984;**140**:773-5.

Cappel R, Beers DV, Liesnard C, Dratwa M. Impaired humoral and cell-mediated immune responses in dialysed patients after influenza vaccination. *Nephron.* 1983;**33**:21-5.

Carroll RNP, Marsh SD, O'Donoghue ENP, Breeze DC, Shackman R. Response to influenza vaccine by renal trasplant patients. *Br Med J* 1974;**2**:701-3.

Cate TR, Couch RB, Parker D, Baxter D. Reactogenicity, immunogenicity, and antibody persistence in adults given inactivated influenza virus vaccines. *Rev Inf Dis* 1983;**5**:737-47.

Central Statistical Office. Social Trends. London: HMSO, 1996.

Centres for Disease Control and Prevention. Follow-up on Guillain-Barré syndrome - United states. MMWR. 1977;26:52.

Centres for Disease Control and Prevention. Reye syndrome - United States. MMWR 1979;28:79.

Centres for Disease Control and Prevention. Increase in pneumonia mortality among young adults and the HIV epidemic in New York City, United States MMWR. 1988;**37**:593-6.

Centres for Disease Control and Prevention. Prevention and control of influenza: Part 1, Vaccines. MMWR 1993;42(RR-6):1-14.

Chakraverty P, Cunningham P, Shen GZ, Pereira MS. Influenza in the United Kingdom 1982 - 85. *Journal of Hygiene* (Cambridge) 1986;**97**:347-8.

Choppin PW, Compans RW. The structure of influenza virus. In: Kilbourne ED, ed. The influenza viruses and influenza. New York: Academic Press, 1975.

Claas ECJ, Jong JC, Bartelds AIM, Bijlsma K, Rothbarth P, Groot R, Rimmelzwaan GF, Osterhaus ADME. Influenza types and patient population. *Lancet* 1995;**346**:180P.

Collins SD. Trend and age variation of mortality and morbidity from influenza and pneumonia. In review and study of illness and medical care with special reference to long-time trend. Public Health Monograph 48, Public Health Service publication 544 U.S. Department of Health, education and welfare, Public Health service 1957.

Committee on influenza and other respiratory virus vaccines. Trials of an Asian influenza vaccine *Br Med J* 1958;**i**:415-8.

Communicable Disease Centre, Influenza Surveillance Report 26, Atlanta, Ga., 1957.

Comstock GW. Vaccine evaluation by case-control or prospective studies. *Am J Epidemiol* 1990;**131**:205-7.

Connolly AM, Salmon RL, Williams DH. What are the complications of influenza and can they be prevented? Experience from the 1989 epidemic of H3N2 influenza A in general practice. *Br Med J* 1993;**306**:1452-4.

Corey L, Rubin RJ, Hattwick MAW, Noble GR, Cassidy E. A nationwide outbreak of Reye's syndrome its epidemiologic relationship to influenza B. *Am J Med* 1976;**61**:615-25.

Couch RB, Webster RG, Kasel JA, Cate TR. Efficacy of purified influenza subunit vaccines and relation to the major antigenic determinants on the haemagglutinin molecule. *J Inf Dis* 1979;**14**:553- .

Creighton C. A history of epidemics in Britain AD 664 - 1666, Cambridge University Press, Cambridge, 1891.

Creighton C. A history of epidemics in Britain, Vols 1 & 2, 2nd ed., Frank Cass, London, and Barnes & Noble, New York 1965.

Crosby AW. Epidemic and Peace, 1918, part IV. Westport, CT: Greenwood press; 1976.

Davenport FM. Reflections on the epidemiology of myxovirus infection. *Med Microbiol Immunol* 1977;**164**:69-76.

David DS, Millian SJ, Whitsell JC, Schwartz GH, Riggio RR, Stenzel KH, Rubin AL. Viral syndromes and renal allograft rejection. *Ann Surg* 1972;**175**:257-9.

Davies JR, Grilli EA. Natural or vaccine induced antibody as a predictor of immunity in the face of natural challenges with influenza viruses. *Epidemiol infect* 1989;**102**:325-33.

Davis LE, Cadwell GG, Lynch RE, Bailey RE, Chin TDY. Hong Kong influenza: the epidemiologic features of a high school family study analysed and compared with a similar study during the 1957 Asian influenza epidemic *Am J Epidemiol* 1970;**92**:240-7.

Department of Health and Social Security. *Administration of radioactive substances to persons.* London: HMSO, 1984. (HN(84)5).

Department of Health and Social Security. *Supervision of ethics of clinical research investigations and fetal research.* London: HMSO, 1975. (HSC (IS) 153.).

Department of Health. Immunisation against infectious disease. London: HMSO, 1992.

Department of Health. *Local research ethics committees.* London, DoH, 1991.

Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med* 1982;**307**:580-4.

Douglas RG Jr. Influenza in man. In Kilbourne ED, ed influenza viruses and influenza. New York: Academic press;1975:395-447.

Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. *JAMA* 1961;**176**:776-82.

Fedson DS, Wajda A, Nicol JP, Hammond GW, Kaiser DL, Roos LL. Clinical effectiveness of influenza vaccination in Manitoba. *JAMA* 1993;**270**:1956-61.

Feery BJ, Evered MG, Morrison E. Different protection rates in various groups of volunteers given subunit influenza virus vaccine in 1976. *J Infect Dis* 1979;**139**:237-41.

Feery J, Evered MG, Morison EI. Different protection rates in various groups of volunteers given sub-unit influenza virus vaccine in 1976. *J Infect Dis* 1979;**139**:237-41.

Fenner F. The classification and nomenclature of viruses. Summary of results of meeting of the International Committee on Taxonomy of Viruses in Madrid, September, 1975. *Virology* 1976;**71**:371-8.

Fleming DM, Chakraverty P, Sadler C, Litton P. Combined clinical and virological surveillance of influenza in winters of 1992 and 1993 - 4. *Br Med J* 1995;**311**:290-1.

Fleming DM, Watson JM, Nicholas S, Smith GE, Swan AV. Study of effectiveness of influenza vaccination in the elderly in the epidemic of 1989 - 90 using a general practice database. *Epidemiol Infect* 1995;**115**:581-9.

Foster DA, Talsma A, Furumoto-Dawson A, Ohmit SE, Margulies JR, Arden NH, Monto AS. Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. *Am J Epidemiol* 1992;**136**:296-306.

Francis T Jr. A new type of virus from epidemic influenza. *Science* 1940;**92**:405.

Francis T Jr. Influenza. In: Viral and Rickettsial infections of man (T. M. Rivers and F Horsfall Jr. ed) 3rd ed. J. B. Lippincott, Philadelphia 1959;633P.

Francis T. Influenza: the newe acquayantance. *Ann Intern Med* 1953;39:203-21.

Freund DA, Dittus RS. Principles of pharmacoeconomics analysis of drug therapy. *PharmacoEconomics* 1992;**1**:20-31.

Gilbert C, Fulford KWM, Parker C. Diversity in the practice of district ethics committees. *Br Med J* 1989;**299**:1437-9.

Glasgow JFT, Moore R. Reye's syndrome 30 years on. Possible marker of inherited metabolic disorders. *Br Med J* 1993;**307**:950-1.

Glezen WP, Couch RB. Interpandemic influenza in the Houston area 1974 - 76. *N Engl J Med* 1978;**298**:587-92.

Glezen WP, Paredes A, Taber LH. Influenza in children. *JAMA* 1980;**243**:1345-49.

Glezen WP, Payne AA, Snyder DN, Downs TD. Mortality and influenza. *J Infect Dis* 1982;**146**:313-21.

Glezen WP. Serious morbidity and mortality associated with influenza epidemics. *Epidemiologic reviews* 1982;**4**:25-35.

Goodeve A, Potter CW, Clark A, Jennings R. A graded-dose study of inactivated, surface antigen influenza B vaccine in volunteers: reactogenicity, antibody response and protection to challenge virus infection. *J Hyg Camb* 1983;**90**:107-15.

Gorell JM, Johnson CC, Rybicki BA. Parkinson's disease and its comorbid disorders: an analysis of Michigan mortality data, 1970 to 1990. *Neurology* 1994;**44**:1865-8.

Govaert ThME, Thijs CTMCN, Masurel N, Sprenger MJW, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. *JAMA* 1994;**272**:1661-5.

Grange JM, Stanford JL, Rook GAW, Wright P. Role of viral infections in the inception of childhood asthma and allergies. *Thorax* 1995;**50**:701P.

Grist NR. Pandemic influenza 1918. *Br Med J* 1979;**2**:1632-3.

Gross PA Quinnan GV, Rodstein M, LaMontagne JR, Kaslow RA, Saah AJ, Wallenstein S, Neufeld R, Denning C, Gaerlan P. Association of influenza immunisation with reduction in mortality in an elderly population. *Arch Int Med* 1988;**148**:562-5.

Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Inter Med* 1995;**123**:518-27.

Gross PA, Lee H, Wolf JA, Hall CB, Minnefore AB, Lazicki RN. Influenza immunisation in immunosuppressed children. *J Pediatr* 1978;**92**:92:30-5.

Gundelfinger BF, Stille WT, Bell JA. Effectiveness of influenza vaccines during an epidemic of an Asian influenza. *N Eng J Med* 1958;**259:**1005-9.

Hall CB, Dolin R, Gala CL, Markovitz DM, Zhano YQ, Madore PH, Disney FA, Talpey WB, Green JL, Francis AB, Pichichero ME. Children with influenza A infection; treatment with rimantadine. *Pediatrics* 1987;**80**:275-82.

Hall SM. Reye's syndrome and aspirin: a review. *Br J Clin Pract* 1990;**44**:4-11.

Hannan SE, May JJ, Pratt DS, Richtsmeier WJ, Bertino JS. The effect of whole virus influenza vaccination on theophylline phamacokinetics. *Am Rev Respir Dis* 1988;**137:**903-6.

Harding NGL, ed. *Data protection in medicine.* NHS Training Authority, Bristol 1986.

Hattori H, Kawamori J, Takao T, Ito M, Nakano S, Okuno T, Mikawa H. Computed tomography in postinfluenzal encephalitis. *Brain Dev* 1983;**5**:564-7.

Hayden FG, Cote KM, Douglas RG. Plaque inhibition assay for drug susceptibility testing of influenza viruses. *Antimicrob Ag Chemother* 1980;**17:**865-70.

Heggeness MH, Smith PR, Ulmanen I, Krug RM, Choppin PW. Studies on the helical nucleocapsid of influenza virus. *J Virol* 1982;**118**:466-70.

Heikkinen T, Waris M, Ruuskanen O. Efficacy of influenza vaccination in reducing otitis media in children. In Options for the control of influenza

II. Edited by Hannoun C, Kendal AP, Klent HD, Ruben FL. Amsterdam: Elsevier;1993:431-4.

Hemmes JH, Winkler DC, Kool SM. Virus survival as a seasonal factor in influenza and poliomyelitis. *Nature* 1960;**188:**430-1.

Hill AB. A short textbook of medical statistics. 11th ed. London: Hodder and Stoughton, 1984.

Hirsch A. Handbook of Geographical and Historical Pathology. V. 1. Translated from the second German edition by Charles Creighton. London: New Sydenham Society, 1883.

Hirst GK. The agglutination of red cells by allantoic fluid of chick embryos infected with influenza virus. *Science* 1941;**94:**22.

Holt P, Kibblewhite K. Acute polymyositis and myoglobinuric renal failure associated with influenza A infection. *NZ Med J* 1995;**108**:436.

Hope-Simpson RE. First outbreak of Hong Kong influenza in a general practice population in Great Britain. A field and laboratory study. *Br Med J* 1970;**3:**74-7.

Hope-Simpson RE. The transmission of epidemic influenza. New York: Plenum, 1992.

Horner GJ, Gray FD. Effect of uncomplicated, presumptive influenza on the diffusing capacity of the lung. *Am Rev Resp Dis* 1973;**108**:866-9.

Horwitz R. Ethical review of multi-centre research. *Bull Med ethics* 1994;Oct:13-15.

Hoskins TW, Davies JR, Allchin A, Miller CL, Pollock TM. Controlled trial of inactivated influenza vaccine containing the A/Hong Kong strain during an outbreak of influenza due to the A/England/42/72 strain. *Lancet* 1973;**2**:116-20.

Hoskins TW, Davies JR, Smith AJ, Allchin A, Miller CL, Pollock TM. Influenza at Christ's hospital: March, 1974. *Lancet* 1976; **i**:105-8.

Hoskins TW, Davies JR, Smith AJ, Miller CL, Allchin A. Assessment of influenza A vaccine after three outbreaks of influenza at Christ's Hospital. *Lancet* 1979;**1**:33-5.

Hotopf M, Wessely S, Noah N. Are ethical committees reliable?. *J R Soc Med* 1995;**88**:31-33.

Howells CHL, Vesselinova-Jenkins CK, Evans AD, James J. Influenza vaccination and mortality from bronchopneumonia in the elderly. *Lancet* 1975;**i**:381-3.

Hsia J, Tang T, Parrott M, Rogalla K. Augmentation of the immune response to influenza by acetylsalicylic acid: clinical trial in a geriatric population. *Meth Find Exp Clin Pharmacol* 1994;**16**:677-83.

Huang KL, Ruben FL, Rinaldo CR, Kingsley L, Lyter DW, Mo M. Antibody responses after influenza and pneumococcal immunization in HIV infected homosexual men. *JAMA* 1987;**257**:2047-50.

Hughey PG, Copmans RW, Zebedee SL, Lamb RAl. Expression of influenza A virus M2 protein is restricted to apical surfaces of polarised epithelial cells. *J Virol* 1992;**66**:5542-52.

Iorio AM, Rivosecchi P, Zei T, Neri M, Merletti L. Immune response to trivalent inactivated influenza vaccine in young and elderly subjects. *Vaccine* 1989;**7**:341-4.

Ishiama A, Toyoda T, Kobayski M. Formation and control of influenza virus RNA polymerase. Options for control of influenza II. Hannoun C, Kendal AP, Klenk HD, eds. Amesterdam: Elsevier; 1993:289-97.

Jamieson WM, Kerr M, Green DM, Sommerville T, Dunbar JM, Boswell J, Duguid H, Gribble MG, Smith GH, Reid JJA, Weir IBL. Some aspects of the recent epidemic of influenza in Dundee. *Br Med J* 1958;**1**:908-13.

Jensen MM. Viruses and kidney disease. *Am J Med* 1967;**43**:897-911.

Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DAJ, Holgate ST.

Community study of role of viral infections in exacerbations of asthma in 9 - 11 year old children. *Br Med J* 1995;**310:**1225-9.

Karadaghi SE, Zakomirdin JA, Shimane C, Bucher DJ, Tverdislov VA, Kharitonenkov IG. Interaction of influenza virus proteins with planar bilayer lipid membranes. 1. Characterisation of their adsorption and incorporation into lipid bilayers. *Biochem Biophys Acta* 1984;**778:**269-75.

Karjalainen J, Nieminen MS, Heikkila J. Influenza A1 myocarditis in conscripts. *Acta Med Scand* 1980;**207**:27-30.

Kava T, Laitenen LA. Effect of killed and live influenza vaccine on symptoms and specific airway conductance in asthmatics and healthy subjects. *Allergy* 1985;**40**:42-7.

Kava T, Lindqvist A, Karjalainen J, Laitenen L. Unchanged bronchial reactivity after killed influenza virus vaccine in adult asthmatics. *Respiration* 1987;**51**:98-104.

Keitel WA, Cate TR, Couch RB. Efficacy of sequential annual vaccination with inactivated influenza virus vaccine. *Am J Epidemiol* 1988; **127:**353-64.

Kendal AP, Galphin JC, Palmer EL. Replication of influenza virus at elevated temperature: Production of virus-like particles with reduced matrix protein content. *Virology* 1977;**76:**186-95.

Kilbourne ED, Schulman JL, Schild GD, Schloer G, Swanson J, Bucher D. Correlated studies of recombinant influenza-virus vaccine. 1. Derivation and characterisation of virus and vaccine. *J Infect Dis.* 1971;**124**:449-62.

Kilbourne ED, Butler WT, Rossen RD. Specific immunity in influenza – summary of influenza workshop III. *J Infect Dis* 1973;**127**:220-6.

Kilbourne ED. Epidemiology of influenza. In: Kilbourne ED, ed. Influenza Viruses and Influenza. New York: Academic Press, 1975.

Kilidireas K, Latov N, Strauss DH, Gorig AD, Hashim GA, Gorman JM, Sadiq SA. Antibodies to the 60kDa heat-shock protein in patients with schizophrenia. *Lancet* 1992;**340:**569-72.

Konto S, Abe K. The effects of influenza virus infection on FEV1 in asthmatic children: the time-course study. *Chest* 1991;**100**:1235-8.

Kramer P, McClain CJ. Depression of aminophylline metabolism by influenza vaccination. *N Engl J Med* 1981;**305:**1262-4.

Kumar S S, Ventura AK, VanderWerf B. Influenza vaccination in renal transplant recipients. *JAMA* 1978;**239:**840-2.

Kumar S S, Ventura AK, Van der Werf B. Influenza vaccination in renal transplant recipients. *JAMA* 1978;**239:**840-2.

Kunugi H, Nanko S, Takei N, Saito K Hayashi N, Kazamatsuri H. Schizophrenia following in utero exposure to the 1957 influenza epidemics in Japan. *Am J Psychiatry* 1995;**152:**450-2.

Kurinczuk JJ Nicholson KG. Uptake of influenza vaccine by patients with serious cardiac disease. *Br Med J* 1989;**299**:367.

Langmuir AD, Worthen TD, Slomon J, Ray CK, Patersen E. The Thucydides syndrome: a new hypothesis for the cause of the plague of Athens. *New Eng J Med* 1985;**313:**1027-30.

Laver WG, Webster RG. Selection of antigenic mutants of influenza viruses: isolation and peptide mapping of their haemagglutinin proteins. *Virology* 1968;**34:**193

Leigh MW. Pathogenesis of respiratory infections due to influenza virus: implications for developing countries. *Rev Infect Dis* 1991;**13 (Suppl)**:501-8.

Lennox IM, Macphee GJA, McAlpine CH, Cameron SO, Leask BGS, Somerville RG. Use of influenza vaccine in long-stay geriatric units. *Age and Ageing* 1990;**19:**169-72.

Lieberman AD, Craven MR. Schizophrenia symptoms alleviated by influenza virus vaccine. *Clin Ecology* 1990;**6:**40-2.

Little JW, Douglas RG Jr, Hall WJ, Roth FK. Attenuated influenza produced by experimental intranasal inoculation. *J Med Virol* 1979;**3:**177-88.

Little JW, Hall WJ, Douglas RG, Mudholkar GS, Speers DM, Patel K. Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. *Am Rev Respir Dis* 1978;**118**:295-303.

Louie JS, Nies KM, Shoji KT, Fraback RC, Abrass C, Border W, Cherry JD, Imagawa D. Clinical and antibody responses after influenza immunisation in systemic lupus erythematosus. *Ann Intern Med* 1978;**88:**790-2.

MacDonald KL, Osterholm MT, Hedberg CW, Schrock CG, Peterson F, Jentzen JM, Leonard SA, Schlievert PM. Toxic shock syndrome newly recognised complication of influenza and influenza-like illness. *JAMA* 1987;**257**:1053-8.

Mackenzie WB, Davis JP, Peterson DE, Hibbard AJ, Becker G, Zarvan BS. Multiple false-positive serologic tests for HIV, HTLV-1 and hepatitis C following influenza vaccination. *JAMA* 1992;**268:**1015-7.

Makinodan T, Kay MMB. Age influence on the immune system. *Adv Immunol* 1980;**29:**287-330.

Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccination in the elderly; a randomised placebo-controlled trial. *JAMA* 1990;**264**:1139-41.

Martin CM, Kunin CM, Gottleib LS, Barnes MW, Liu C, Finland M. Asian influenza A in Boston, 1957 - 1958. *Arch Intern Med* 1959;**103**:515-43.

Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective. *Thorax* 1994;**49:**1189-91.

Masurel N, Heijtink RA. Recycling of H1N1 influenza A virus in man: a haemagglutinin antibody study. *J Hyg* 1983;**90:**307-402.

Masurel N, Marine WM. Recycling of Asian and Hong Kong influenza A virus haemagglutinins in man. *Am J Epidemiol* 1973;**97**:44-9.

Masurel N, Ophof P, De Jong P. Antibody response to immunization with influenza A/USSR/77 (H1N1) virus in young individuals primed or unprimed for A/New Jersey/76 (H1N1) virus. *J Hyg Camb* 1981;87:201-9.

McDonald JC, Andrews BE. Diagnostic methods in an influenza vaccine trial. *Br Med J* 1955;**2**:1232-5.

McIntyre PG, Doherty C. Acute benign myositis during childhood: report of five cases. *Clin Infect Dis* 1995;**20**:722.

McKelvie PA. Medical certification of causes of death in an Australian Metropolitan hospital. Comparison with autopsy findings and a critical review. *Med J Aust* 1993;**158**:816-21.

Ministry of Health. Report on the pandemic of influenza, 1918-19 Reports on Public Health and Medicine, No. 4, HMSO, London, 1920.

Ministry of Health. *Supervision of the ethics of clinical research.* London: HMSO, 1968. (HM(68)33.)

Ministry of Health. The influenza epidemic in England and Wales, 1957 - 1958. HMSO, London, 1960.

Miotti PG, Nelson KE, Dallabetta GA, Farzadegan H, Margolick J, Clements ML. The influence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine. *JAMA* 1989;**262**:779-83.

Mogabgab WJ. Virus association with upper respiratory illness in adults. *Ann Intern Med* 1963;**59**:306-22.

Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P. Severe community-acquired pneumonia, Etiology, Epidemiology, and prognosis Factors. *Chest* 1994;**105**:1487-95.

Molsa P, Marttila R, Rinne U. Survival and cause of death in Alzheimer's disease and multiinfarct dementia. *Acta Neurol Scand* 1986;**74**:103-7.

Monto AS, Koopman JS, Longini Jr IM. Tecumseh study of illness XIII. Influenza infection and disease, 1976 - 1981. *Am J Epidemiol* 1985;**121**:811-22.

Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and agents involved. *Epidemiol Infect* 1993;**110**:145-60.

Moran J. Local research ethics committees, report of the second national conference. *J R Coll Phys Lond* 1992;**26(4)**:423-31.

Moss SE, Klein R, Klein BEK. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991;**81**:1158-62.

Mullooly J, Bennett M, Hornbrook M, Barker W, Williams W, Patriarca P. Influenza vaccination program for elderly persons: cost-effectiveness in a health maintenance organisation. *Ann Intern Med* 1994;**121**:947-52.

Nelson KE, Clements ML, Miotti P, Cohen S, Polk BF. The influence of human immunodefeceincy virus (HIV) infection on antibody response to influenza vaccine. *Ann Intern Med* 1988;**109**:383-8.

Neuberger J. *Ethics and health care: the role of research ethics committees in the United Kingdom*. London: King's fund institute, 1992.

Nguyen-Van-Tam JS, Nicholson KG. Influenza deaths in Leicestershire during the 1989/90 epidemic: implications for prevention. *Epidemiol Infect* 1992;**108**:537-45.

Nguyen-Van-Tam JS, Nicholson KG. Influenza immunisation: policies and practices of general practioners in England: 1991/92. *Health Trends* 1993;**25**:101-5.

Nguyen-Van-Tam JS, Nicholson KG. Influenza immunisation; vaccine offer, request and uptake in high-risk patients during the 1991/2 season. *Epidemiol infect* 1993;**111**:347-55.

Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Eng J Med* 1994;**331:**778-84.

Nicholson KG. Influenza vaccination and the elderly. *Br Med J* 1990;**301:**617-8.

Nicholson KG. Immunisation against influenza among people aged 65 living at home in Leicestershire during winter 1991-2. *Br Med J* 1993;306:974-6.

Nicholson KG, Tyrrell DAJ, Harrison P, Potter CW, Jennings R, Clark A. Clinical studies of monovalent inactivated whole virus and sub-unit A/USSR/77 (H1N1) vaccine; serological response and clinical reactions. *J Biol Stand* 1979;**7**:123.

Nicholson KG, Wiselka MJ, May A. Influenza vaccination of the elderly: perceptions and policies of general practitioners and outcome of the 1985 - 86 immunisation program in Trent, UK. *Vaccine* 1987;**5:**302-6.

Nicholson KG, Snacken R, Palache AM, Influenza immunisation policies in Europe and the United States. *Vaccine* 1995;**13**:365-9.

Norusis MJ, SPSS INC. SPSS-PC+ V 2.0 Base manual. Chicago: SPSS Inc., 1988.

O'Brien WA, Grovit-Ferbas K, Namazi A, Ovcak-Derzic S, Wang H, Park J, Yeramian C, Mao S, Zack JA. Human immunodeficiency virus-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. *Blood* 1995;**86:**1082-9.

OPCS Monitor PP2 89/2 Office of Population Census and Surveys. London: HMSO, 1989.

OPCS. Cancer statistics registration. London: HMSO, 1987.

Ortbals DW, Liebhaber H, Presant CA, Van Amburg AL, Lee JY. Influenza immunisation of adult patients with malignant diseases. *Ann Intern Med* 1977;**87**:552-7.

Oseasohn R, Adelson L, Kaji M. Clinicopathologic study of thirty-three fatal cases of Asian influenza. *N Eng J Med* 1959;**260**:509-18.

Oswald NC, Shooter RA, Curwen MP. Pneumonia complicating Asian influenza. *Br Med J* 1958;**ii:**1305-11.

Ouellette JJ, Reed CE. Increased response of asthmatic subjects to methacholine after influenza vaccine. *J Allergy* 1965;**36**:558-63.

Pabico RC, Douglas RG, Betts RF, McKenna BA, Freeman RB. Influenza vaccination of patients with glomerular diseases. *Ann Intern Med.* 1974;**81:**171-7.

Pabico RC, Douglas RG, Betts RF, McKenna BA, Freeman RB. Antibody response to influenza vaccination in renal transplant patients: correlation with allograft function. *Ann Intern med* 1976;**85**:431-6.

Pandemic Working Group of Medical Research Council's Committee on Influenza and other Respiratory Virus Vaccines. Antibody responses and reactogenicity of graded doses of inactivated influenza A/New Jersey/76 whole-virus vaccine in humans. *J Infect Dis* 1977;**136 (Suppl)**:475.

Parsons HF. Report on the influenza epidemic of 1889/90. Local Government Board, HMSO, London, 1891.

Patriarca PA, Kendal AP, Stricof RL, Weber JA, Meissner MK, Dateno B. Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med* 1983;**308:**1601-2.

Patriarca PA, Weber JA, Parker RA, Hall WN, Kendal AP, Bregman DJ, Schonberger LB. Efficacy of influenza vaccine in nursing homes. reduction in illness and complications during an influenza A (H3N2) epidemic *JAMA* 1985;**253**:1136-9.

Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalizations as a measure of impact of epidemic influenza. *Am J Epidemiol* 1985;**122:**468-76.

Pons MW, Schulze IT, Hirst GK. Isolation and characterisation of the ribonucleoprotein of influenza virus. *Virology* 1969;**39:**250-9.

Powers DC, Belshe RB. Effect of age on cytotoxic T lymphocyte memory as well as serum and local antibody responses elicited by inactivated influenza virus vaccine. *J Infect Dis* 1993;**167**:584-92.

Protheroe SM, Mellor DH. Imaging in influenza A encephalitis. *Archives of Diseases in Childhood* 1991;**66**:702-5.

Pryor HB. Influenza: that extraordinary malady. Notes on its history and epidemiology. *Clin Pediatr* 1964;**3**:19-24.

Public Health Laboratory. Deaths from Asian influenza, 1957. *Br Med J* 1958;**ii**:915-8.

Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. *J Infect Dis* 1980;**142**:844-9.

Quenel P, Dab W, Hannoun C, Cohen JM. Sensitivity, specificity and predictive values of health service based indicators for surveillance of influenza A epidemic. *Inter J Epidemiol.* 1994;**23**:847-55.

Ragni MV, Ruben FL, Winkelstein A, Spero JA, Bontempo FA, Lewis JH. Antibody responses to immunization of patients with haemophilia with and without evidence of human immunodefeiceincy virus (human T lymphotrophic virus type III) infection. *J Lab Clin Med* 1987;**109**:545-9.

Raj G, Kumar R, McKinney WP. Safety of intramuscular influenza immunisation among patients receiving long-term warfarin anticoagulation therapy. *Arch Intern Med* 1995;**155**:1529-31.

Rappaport RS, Dodge GT. Prostaglandin E inhibits the production of human interleukin-2. *J Exp Med* 1982;**155**:943-8.

Rekart M, Rupnik K, Cesario TC, Tilles JG. Prevalence of haemagglutinin inhibition antibody to current strains of the H3N2 and H1N1 subtype of influenza A virus in sera collected from the elderly in 1976. *Am J Epidemiol* 1982;**115**:587-97.

Renton KW, Gray JD, Hall RI. Decreased elimination of theophylline after influenza vaccination. *Can Med Assoc J* 1980;**123:**288-90.

Rey O, Nayak DP. Nuclear retention of M1 protein in a temperature-sensitive mutant of influenza (A/WSN/33) virus does not affect nuclear export of viral ribonucleoproteins. *J Virol* 1992;**66**:5815-24.

Riddiough MA, Sisk JE, Bell JC. Influenza vaccination. Cost-effectiveness and public policy. *JAMA* 1983;**249:**3189-95.

Ristow SC, Douglas RG, Condemi JJ. Influenza vaccination of patients with systemic lupus erythematosus. *Ann Intern Med* 1978;**88:**786-89.

Romano PS, Luft HS. Getting the most out of messy data: problems and approaches for dealing with large administrative data sets. In: Grady ML, ed. *Medical effectiveness Research Data Methods*. Rockville, Md: Agency for Health Care Policy and Research; 1992:57-75.

Rott R, Klenk HD, Nagai Y, Tashiro M. Influenza viruses, cell enzymes and pathogenicity. *Am Respir Crit Care Med* 1995;**152 (Suppl)**:16-19.

Royal College of Physicians. *Supervision of the ethics of clinical research investigations in institutions.* London: HMSO, 1967(updated 1973).

Royal College of Physicians. *Guidelines on the practice of ethics committees in medical research.* London: RCP, 1984.

Royal College of Physicians. Research on healthy volunteers. *J R Coll Physicians Lond* 1986;**20:**243-7.

Royal College of Physicians. *Guidelines on the practice of ethics committees in medical research involving human subjects.* London: RCP, 1990.

Salvetti M, Pisani A, Bastianello S, Millefiorini E, Buttinelli C, Pozzilli C. Clinical and MRI assessment of disease activity in patients with multiple sclerosis after influenza vaccination. *J Neurol* 1995;**242:**143-6.

Scheiblauer H, Reinacher M, Tashiro M, Rott R. Interactions between bacteria and influenza A virus in the development of influenza pneumonia. *J Infect Dis* 1992;**166**:783-91.

Scholtissek C, von Hoyningen V, Rott R. Genetic relatedness between the new 1977 epidemic strains (H1N1) of influenza and human influenza strains isolated between 1947 and 1957. *Virology* 1978;**89**:613-.

Schwarzmann SW, Alder JL, Sullivan RJ, Marine WM. Bacterial pneumonia during the Hong Kong influenza epdemic of 1968 - 1969. *Arch Intern Med.* 1971;**127**:1037-41.

Shope RE. Influenza. History, epidemiology, and speculation. The R. E. Dyer Lecture. *Public Health Rep* 1958;**73:**165-78.

Sibley WA, Bamford CR, Laguna JF. Influenza vaccination in patients with multiple sclerosis. *JAMA* 1976;**236:**1965-6.

Skehel JJ, Wiley DC. Influenza viruses and cell membranes. *Am J Respir Crit Care Med* 1995;**152 (S)**:513-15.

Smith PG, Rodrigues LC, Fine PEM. Assessment of the protective efficacy of vaccines against common diseases, using case-control and cohort studies. *Int J Epidemiol,* 1984; **13:**87-93.

Smith W, Andrews CH, Laidlaw PP. A virus obtained from influenza patients. *Lancet* 1933;**2:**66.

Spelman DW, McHardy CJ. Concurrent outbreaks of influenza A and influenza B. *J Hyg Camb* 1985;**94**:331-9.

Stenius-Aarniala B, Huttunen JK, Pyhala R, Haahtela T, Jokela P, Jukkara A, Karakorpi T, Katoja M, Kava T, Kuusisto P, Lahdensuo A, Mansury L, Niemistö M, Taivainen A, Vaara S, Vesterinen E. Lack of clinical exacerbations in adults with chronic asthma after immunization with killed influenza virus. *Chest* 1986;89:786-9.

Strassburg MA, Greenland S, Sorvillo FJ, Lieb LE, Habel LA. Influenza in the elderly: report of an outbreak and a review of vaccine effectiveness reports. *Vaccine* 1986;**4:**38-44.

Strikas R, Cook P, Kuller L, Talbotte E, Ploufe J, File T, Poggio E, Kidder D, Baughman A, Manorharan A, Hutton E. Case-control study in Ohio

and Pennsylvania on prevention of hospitalization by influenza vaccination. Options for control of influenza II. Edited by Hannoun C, Kendal AP, Klenk HD, Ruben FL. Amsterdam: Elsevier; 1993:153-60.

Stuart-Harris CH, Schild GC, Oxford JS ed: Influenza, the viruses and the disease, Edward Arnold, London, 1985.

Stuart-Harris CH. Pandemic influenza: an unresolved problem in prevention. *J Inf Dis.* 1970;**122:**108-115.

Sydenham T. Influenza: Of the epidemic disease. In Major RH, ed Classical descriptions of Disease. Springfield, IL: Charles C Thomas; 1955;201P.

Taber LH, Paredes A, Glezen WP, Couch RB. Infection with influenza A/Victoria virus in Houston families, 1976. *J Hyg Camb* 1981;**86:**303-13.

Takei N, Sham P, O'Callaghan E, Murray GK, Glover G, Murray RM. Prenatal exposure to influenza and the development of schizophrenia: is the effect confined to females. *Am J Psychiatry* 1994;**151:**117-19.

Taylor RM. A further note on 1233 ("influenza C") virus. *Arch Gesamte Virusforsch* 1951;**4:**485.

The Institute of Health services Management. *Hospital Year Book.* Guy Howland, London 1991.

Theodorides J. The plague of Athens. *J Royal Society of Med* 1995;**88**:363P.

Thompson IE, French K, Melia K, Boyd KM, Templeton AA, Potter B. Research ethics committees in Scotland. *Br Med J* 1981;**282**:718-20.

Thompson T. Annals of influenza or epidemic catarrhal fever in Great Britain from 1510 to 1837. Sydenham Society, London, 1852.

Tillett HE, Smith JWG, Gooch CD. Excess deaths attributable to influenza in England and Wales: age at death and certified cause. *Int J Epidemiol* 1983;**12:**344-56.

Tolan RW Jr. Toxic shock syndrome complicating influenza A in a child: case report and review. *Clin Infect Dis* 1993;**17**:43-5.

Van Voris LP, Betts RF, Hayden FG, Christmas WA, Douglas RG. Successful treatment of naturally occurring influenza A/USSR/77 H1N1. *JAMA* 1981;**245:**1128-31.

Versluis DJ, Beyer WEP, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by Cyclosporine, but not Azathioprine. *Transplantation* 1986;**42**:376-9.

Versluis DJ, Beyer WEP, Masurel N, Weimar W. Value of booster immunisation with influenza vaccine in patients undergoing haemodialysis. *Br Med J* 1987; **294**:348P.

von Itzstein M, Wu WY, Kok GB, Pegg MS, DyasonJC, Jin B, Phan TV, Smythe ML, White HF, Oliver SW, Colman PM, Varghese JN, Ryan DM, Woods JM, Bethell RC, Hotham VJ, Cameron JM, Penn CR. Rational design of potent sialidase-based inhibitors of influenza virus replication. *Nature* 1993;**363:**418-23.

Waldman RJ, Hall WN, McGee H, George VA. Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982;**247**:3089-94.

Webster PG, On the origin of pandemic influenza viruses. *Curr Top Microbiol Immunol* 1972;**29:**75-

Webster RG, Laver WG, Air GM, Ward C, Gerhard W, van Wyke KL. The mechanism of antigenic drift in influenza viruses: analysis of Hong Kong (H3N2) variants with monoclonal antibodies to the haemagglutinin molecule. *Ann NY Acad Sci.* 1980;**354:**162-8.

Wells CEC. Neurological complications of so-called influenza A winter study in South Wales. *Br Med J* 1971;**1**:369-73.

Wenzel RP, Hendly O, Sande MA, Gwaltney JM. Serum and nasal antibody response to parenteral vaccination. *JAMA* 1973;**226**:435-8.

Wiley DC, Wilson IA, Skehel JJ. Structure identification of antibody binding sites of Hong Kong influenza haemagglutinin and their involvement in antigenic variation. *Nature* 1981;**289**:373-8.

Williams GW, Steinberg AD, Reinertsen JL, Klassen LW, Decker JL, Dolin R. Influenza immunisation in systemic lupus erythematosus: A double-blind trial. *Ann Intern Med* 1978;**88**:729-34.

Winterbawer RH, Ludwig WR, Hammer SP. Clinical course, management and long term sequelae of respiratory failure due to influenza viral pneumonia. *Johns Hopkins Med J* 1977;**141**:148-55.

Wiselka MJ, Nicholson KG, Kent J, Stern M. Influenza and asthma. *Lancet* 1992;**339**:367-8.

Woodall J, Rowson KEK, McDonald JC. Age and Asian influenza. *Br Med J* 1958;**4**:1316-18.

Woods JM, Bethell RC, Coates JAV, Healy N, Hiscox SA, Pearson BA, Ryan DM, Ticehurst J, Tilling J, Walcott SM, Penn CR. 4-Guanidino-2,4-Dideoxy-2,3-Dehydro-*N*-Acetylneuraminic acid is ahighly effective inhibitor both of the sialidase (neuraminidase) and of growth of a wide range of influenza A and B viruses in vitro. *Anti Microb Agent and Chemotherapy* 1993;**37(7)**:1473-9.

Working Party on Ethics of Research in Children. Guidelines to aid ethical committees considering research involving children. *Br Med J* 1980;**280**:229-31.

World Health Organisation. *World Health Organisation Statistics Annuals.* World Health Organisation, Geneva, 1977 - 1989.

Wright P, Murrary RM. Schizophrenia: prenatal influenza and autoimmunity. *Ann Med* 1993;**25**:497-502.

Yeldani AV, Colby TV, Pathologic features of lung biopsy specimens from influenza pneumonia cases. *Hum Pathol* 1994;**25**:47-53.

Zumwalt RE, Ritter MR. Incorrect death certification: An invitation to obfuscation. *Postgraduate Medicine* 1987;**81**:245-54.