

## SECTION 5

# FUTURE PROSPECTS FOR THE CONTROL OF INFLUENZA BY IMMUNOPROPHYLAXIS AND CHOICE OF GROUPS FOR ROUTINE VACCINATION

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## Vaccination in the control of influenza

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### Summary

Although killed influenza vaccine given by injection is protective, able to reduce sickness absence in industry and to control influenza in the armed forces, it has not so far been possible to demonstrate more than a small effect on the disease in otherwise healthy adults in industry and offices in the United Kingdom. The reasons are probably the poor rate of acceptance of vaccine, the relatively low incidence of clinical influenza in most years, and the incomplete protection given by the vaccine. Until major epidemics can be accurately forecast it is suggested that influenza vaccination may most usefully be used on a selective basis, namely for protecting those with illness predisposing to a severe effect from influenza; persons in institutions such as schools and homes for the elderly; key workers in the general population; and persons over the age of 65 years among whom considerable mortality occurs in winters when influenza is prevalent.

At the present time in the U.K. the use of inactivated vaccines offers the only serious possibility of controlling epidemic influenza, and although live attenuated vaccines given nasally may eventually prove to be more suitable they are not at present available. Davenport and others have concluded that injected inactivated vaccines may allow the control of influenza in communities where a high vaccine acceptance can be maintained as, for example, in the armed forces (Davenport, 1966, 1970). Furthermore, the vaccines available nowadays contain more antigen and may

be of greater purity than those used in the studies referred to by Davenport (1970), so that their effectiveness in wide-scale use may be greater. Improvements in surveillance, and in laboratory techniques for deriving rapidly-growing variants from fresh virus strains, increase the likelihood that vaccines adapted to pandemic influenza viruses may in future become available in time to be of practical value. However, during the last few years the value of influenza vaccination in the control of influenza in factories and offices has been under study from the Epidemiological Research Laboratory (E.R.L.) and the evidence so far available suggests that, although vaccination may reduce sickness absence, vaccines given by injection have only a limited role to play in the control of influenza.

### The effectiveness of vaccine in healthy adults in industry

In a factory population, influenza vaccination was offered on 29 November, 1972 (week 47). Volunteers were given by random allocation either bivalent vaccine containing A/Northern Territories/6/68, 400 i.u. and B/Rome/1/67, 200 units, or monovalent vaccine containing B/Victoria/98926/70, 400 i.u. by i.m. injection. Medically-certificated sickness absence (i.e. 3 days and over) in the two groups, and also in the remainder of the factory population, was recorded from week 48, 1972 to week 22, 1973. The findings, excluding employees who were absent at any time in

TABLE 1. Certificated sickness absence \* in factory employees, 1972-73

Category of employees	No. of employees	Average no. of days lost from sickness absence/100 employees/week		
		Influenza period†	Non-influenza period‡	Excess in influenza period
Vaccinated A + B	646	4.6	2.4	2.2
Vaccinated B	524	6.9	2.8	4.1
Non-vaccinated	3280	7.9	3.9	4.0

\* Excluding absentees in week of vaccination and absences over 9 weeks' duration.

† Influenza period (Estimated from returns to E.R.L. from P.H.L.S. and other laboratories) = weeks 48, 1972 to 9, 1973.

‡ Non-influenza period = weeks 36-45, 1972 to 10-22, 1973.

TABLE 2. Vaccination study in the Post Office. Days lost from sickness absence/week/100 employees

		1971/72		1972/73		1973/74	
		'Vacc.*	Unvacc.†	'Vacc.'	Unvacc.	'Vacc.'	Unvacc.
Excess in influenza period‡ compared with non-influenza period	Telecomms	4.1	6.4	8.0	6.3	2.3	2.3
	Posts	-	-	3.6	5.1	3.4	4.4
Average over whole study period	Telecomms	22	22	25	24	21	23
	Posts	-	-	29	31	30	32

\* 'Vacc.' = group of employees offered vaccination.

† Unvacc. = group of employees not offered vaccination.

‡ Influenza period estimated from returns to E.R.L. by P.H.L.S. and other laboratories.

the week in which the vaccinations were given and also those with absences of more than 9 weeks' duration, are shown in Table 1. From early December, 1972 to the end of February, 1973 influenza due to the A/England/42/72 virus was prevalent in Britain, and very little illness was caused by the influenza B virus (information from returns to the E.R.L. by Public Health Laboratory Service (P.H.L.S.) and other laboratories). Although the A/England virus had drifted in its antigenic structure from the A/Hong Kong-like strain in the vaccine, sickness absence among volunteers who had received the bivalent vaccine was less during the influenza period than that of the volunteers given influenza B vaccine. Those who had vaccine containing influenza A experienced an average of 2.2 days/100 employees/week more sickness absence during the influenza period than in the succeeding non-influenza period, compared with 4.1 days more among those who had the monovalent B vaccine. Thus the findings suggest that vaccination effected a saving of 1.9 days/100 employees/week during the influenza period. This saving was small but was consistent with data on the incidence of influenza among the working-age population in the epidemic (see below).

The findings suggest that influenza vaccination in industrial employees is capable of reducing sickness absence. However, a comparison of absence rates among factory volunteers who agree to take part in an influenza vaccine study will not necessarily reflect the value of an offer of vaccine in a whole factory

population—of whom more than two-thirds are likely to be non-volunteers. Thus, as may be seen in Table 1, absence among those accepting vaccine tends to be lower than among those who do not even during months when there is no influenzal illness (Smith *et al.*, 1974b). A study designed to avoid such difficulties is in progress in collaboration with the British Post Office.

### The Post Office study

In this study approximately 50,000 Post Office employees working in telecommunications units, sorting and other offices in many different parts of Great Britain are offered influenza vaccine by injection at the beginning of the winter. The sickness absence of the whole group, i.e. including employees who do and those who do not have an injection of vaccine, is then compared during the winter for a 5-month period with that of a matched group of 50,000 employees who are not offered vaccine (Smith, 1974). The study is now in its fourth winter and is planned to be continued for a total of five winters. The comparison allows a valid estimate to be made of the overall effect of vaccination on absence since many units in different parts of the country are being compared, i.e. the two groups are both matched and equally exposed to influenza. Table 2 gives findings from the first 3 years of the study.

In the first winter, 1971/72, observations were made in the telecommunications branch only and concerned two groups each of about 26,000 persons.

TABLE 3. Acceptance rate of influenza vaccine in industrial workers

Factory	Nature of factory	1971/2	1972/3	1973/4	1974/5
Post Office					
Telecomms	Skilled technical	42%	34%	35%	32%
Posts	Postmen and counter staff	—	36%	28%	23%
A	Light industry and office	40%	26%	22%	19%*
B	Light industry and office	42%	27%	20%	14%
C	Office staff	—	32%	26%	27%*

\* Based on 1973/4 total population.

In the period when influenza was prevalent, sickness absence rates were lower in the units offered vaccination than in the units not offered vaccination; thus the excess absence in the influenza period (i.e. excess over that in the weeks of observation when influenza was not prevalent) was 4.1 days/100 employees/week in the vaccinated units and 6.4 days/100 employees/week in the units not offered vaccination. This apparent saving, however, was offset by the experience of the two groups outside the influenza period, when the units offered vaccination had higher sickness absence rates than the unvaccinated units. Consequently over the whole 21-week period of observation there was no difference in the sickness absence experience of the two groups. In the following years, 1972/73 and 1973/74, Posts employees also took part. The results given in Table 2 show that only a small saving in sickness absence could be detected in the groups of units where vaccination had been offered; indeed in telecommunications in 1972/73 the excess sickness absence in the influenza period was greater in the group of units offered vaccination. The average saving in sickness absence has been approximately 7 days per 100 employees in each winter's influenza period—during which about 270 days are lost by each 100 employees.

#### Consideration of the factors influencing the effect of influenza vaccination in industry

It is evident from the results given above that in the last 3 years in the U.K. an offer of influenza vaccine to healthy adults in the Post Office has had only a small benefit on sickness absence rates. The explanation probably lies in a number of contributing factors.

##### (1) Acceptance rate

The percentage of employees accepting vaccination in a number of different factories and offices in the last three to four winters is given in Table 3. The offer of vaccine was made by letter to every employee and was accompanied by favourable publicity from the industrial medical officer, and was supported by pamphlets and posters pointing out the value of influenza vaccination, and coincidentally in each year there was also much favourable publicity in

national media supporting influenza vaccination. It is apparent that the highest acceptance rates secured in these studies was 42%, a rate seen only in the first winter of an offer of vaccine. Thereafter acceptance has fallen—in factory B to 14% in 1974/75. The average acceptance rate in all these studies was 32%. The findings suggest that a relatively small proportion of workers in the U.K. at the present time are prepared to accept an injection of influenza vaccine, and that when the offer is repeated in successive winters the acceptance rate is liable to decline.

The reasons for the low acceptance rates have been examined by means of a questionnaire to 5174 industrial workers who refused influenza vaccine. Approximately 60% completed and returned the questionnaire, and a variety of reasons were given for refusal of vaccine, including apathy (25%), disbelief in the effectiveness of vaccine (26%) and fear of adverse reactions (28%). Furthermore, in subjects who were vaccinated in 1972 but who had refused in 1973, 48% did so because they had previously experienced untoward symptoms following influenza vaccination. We therefore believe that untoward symptoms after influenza vaccination are an important factor contributing to the decline in acceptance of influenza vaccine in successive winters, although it should be stressed that most reactions are minor in nature and not of clinical significance (Smith, Fletcher and Wherry, 1974a).

The highly purified influenza vaccines developed in recent years may give a higher vaccine acceptance rate in healthy adults because they may produce fewer adverse reactions (Mostow *et al.*, 1969). A study was made of reactions to a detergent-split, zonally purified monovalent A/Port Chalmers/5/73 vaccine which, on electron microscopy, showed the presence of only haemagglutinin and neuraminidase (Dr I. Furminger, personal communication). The vaccine was adsorbed with aluminium hydroxide and it was therefore compared both with standard zonally-purified vaccine and with standard vaccine adsorbed with the same concentration of aluminium adjuvant. The vaccines, each containing 400 units in 0.5 ml, were given by random allocation to healthy adult factory workers. Reactions were recorded by asking the vaccinees to complete a simple enquiry

form recording each day for 5 days the presence or absence of symptoms. 'Subjective' reaction rates found by this method tend inevitably to be high (Smith *et al.*, 1974a). The incidence of subjective reactions, mostly minor in nature, did not vary widely between the three groups (Table 4), but an absence of side effects was reported by 40% of the split vaccine recipients, compared with 34% of those given the other vaccines. However, the incorporation of adjuvant in highly purified vaccines may overcome the presumed lower reactivity of the purified antigens since local reactions were recorded by 42% of those given the purified adsorbed vaccine compared with only 25% of those receiving standard non-adsorbed vaccine. Whilst it is possible that clinically significant reactions may be reduced in frequency to a small extent by means of highly purified split vaccines, these findings suggest that the use of purified vaccines is unlikely greatly to improve vaccine acceptance among healthy adults.

TABLE 4. Subjective reactions in volunteers randomly allocated to receive one of three influenza vaccines, 400 units in 0.5 ml i.m.

Vaccine	% with subjective reactions		
	None	Local	General
Split, purified, adsorbed (73 persons)	40	42	42
Non-split, adsorbed (71 persons)	32	55	37
Non-split, not adsorbed (71 persons)	35	25	46

It may also be considered that nasal influenza vaccines might be more acceptable to healthy adults, since an injection is avoided. A study was made of the subjective reactions to live attenuated vaccine

given as nose drops, inactivated nasal spray vaccine, and injected vaccine in healthy students given the vaccines by random allocation. The incidence of subjective reactions was found to be greater after injected vaccine (Table 5), owing to occurrence of local reactions at the site of injection. It is therefore possible that acceptance rates may be higher with the use of vaccines given by nose.

## (2) The influenza attack rate

An influenza surveillance study carried out by the Public Health Laboratory Service (P.H.L.S.) in collaboration with family doctors enables an estimate to be made of the proportion of the population suffering an attack of clinical influenza each year. A total of 140,000 patients are under observation by their family doctors and P.H.L.S. virologists. The number of consultations for acute respiratory illness during the winter are recorded each week, and swabs for virus isolation are collected from a proportion of these patients. The number of swabs from which an influenza virus is isolated may be related to the number of patients ill with respiratory disease to give an estimate of the proportion of respiratory illness due to influenza. This 'virologically-estimated influenza rate' must presumably underestimate the true incidence of clinical influenza because influenza virus isolation is not always successful, but there is reason to believe from P.H.L.S. studies that virus isolation is probably successful in at least one-third of clinical cases. Consequently, the rate of influenza sufficiently severe to cause patients to consult their family doctors probably lies between one and three times that given by the 'virologically-estimated rate'. The 'virologically-estimated' incidence of clinical influenza in the working-age population in the last two winters (1972/73; 1973/74) was only about 1% (Table 6), so that the actual incidence among the

TABLE 5. Subjective reactions in 247 vaccinees

	Type of vaccine			
	Injected	Killed nasal	Attenuated nasal	
			First dose	Second dose
Number vaccinated	89	78	80	75
% with no reactions	3	36	43	67
% with general reaction	63	63	57	33
% with local reaction	92	—	—	—

TABLE 6. 'Virologically estimated' incidence of clinical influenza by age group

Year	Percentage of patients consulting with respiratory disease from whom influenza virus was isolated, by age group (years)						
	0-4	5-14	15-24	25-44	45-64	65+	15-64 (i.e. working age)
1972/3	3.1	1.3	1.5	1.1	1.0	1.3	1.2
1973/4	3.1	2.9	1.1	1.0	0.9	0.9	1.0

working-age population of influenza sufficiently severe to lead to consultation with their general practitioners was probably only about 2% each winter.

An estimate of the attack rate may also be obtained by relating the excess numbers of new sickness benefit claims in a winter (e.g. excess over that recorded in the winter of 1970/71, when there was virtually no influenza in Britain) to the total working age population insured for sickness benefit. Thus, for example, the number of new sickness benefit claims in 1972/73 in England, Wales and Scotland was 0.6 million more than in 1970/71. The insured population was approximately 19.2 million in 1972/73. Thus, even if all the excess claims were due to influenza, only 3% of the working population would have had an attack severe enough to cause a benefit claim. The relationship between the number of excess claims and the actual number of cases of influenza is uncertain, but the estimate it provides is of the same order as that given by the surveillance study, and supports the evidence that the incidence of clinical influenza has not been high in recent winters. It should be mentioned that the population on which the P.H.L.S. estimate is based differs from that liable to sickness benefit, mainly because many married women are not insured.

Further information is available from a second P.H.L.S. study in collaboration with the Royal College of General Practitioners. Volunteer patients provide blood samples twice a year and have all respiratory and non-specific febrile illnesses investigated, i.e. the volunteers consult their doctors even for minor and trivial respiratory and non-specific illnesses, including those for which normally they would not trouble their family doctors. A total of 325 volunteers were under observation in 1973/74, and influenza virus was isolated from the nose and throat of nine (3%) who had a respiratory or minor febrile illness. Of these nine patients three were insufficiently ill to require bed-rest, leaving six (2%) who had a virologically-proved attack of influenza which would probably have caused them to have consulted their doctor in the normal course of events.

These observations taken together suggest that the number of cases of influenza occurring among people of working age in 1972/73 and 1973/74 was only of the order of 2% and the available evidence suggests that the proportion ill in 1971/72 was similar, i.e. there have been relatively few cases of influenza to prevent in recent winters.

### (3) Degree of protection given by influenza vaccine

Studies of the effect of an injection of influenza vaccine indicate that protection is incomplete, the reported figures varying perhaps between about 40% and 80% (Davenport, 1970; de Casparis, Masurel

and Kerrebijn, 1972; Hoskins *et al.*, 1973; Stiver *et al.*, 1973), probably depending on such factors as the closeness of the relationship between the vaccine virus antigens and those to which the vaccinated population is exposed, and the concentration of antigen in the vaccine.

The poor effect of influenza vaccination on sickness absence in the Post Office in the last 3 years may thus be attributed to at least three factors—poor acceptance of vaccine, a low attack rate, and incomplete protective effect of the vaccine. If, for example, only 30% of employees accept a vaccine that is 70% protective and they are subsequently exposed to an outbreak in which 3% suffer an attack of clinical influenza, it is to be expected that over a whole winter period less than one illness per 100 employees could be prevented. Such an estimate accords with the findings of the Post Office study.

### The place of injected vaccine in the control of influenza

The evidence we have considered suggests that the use of injected influenza vaccine in healthy adults is unlikely to give great benefit in many winters. Appreciable benefits are only to be expected in years when there is a large influenza outbreak, provided a high proportion of susceptible people accept a vaccine that contains the appropriate protective antigens. Although it might in future become possible to predict the occurrence of the larger epidemics, this is not at present feasible and the question should be considered as to how influenza vaccine can best be used. The present advice of the Department of Health (1974) in the U.K. is to offer vaccination to those at special risk, i.e. people with certain illnesses such as chronic chest disease, and they also recommend that vaccine could usefully be used in institutions, e.g. schools and old people's homes. This policy would seem on the available evidence to have much to recommend it, but the possibility may also be considered whether a greater effort to vaccinate elderly persons might be justified in the U.K. Studies in the U.S.A. have suggested that much of the excess mortality that is recorded during influenza winters occurs in the elderly (Eickhoff, Sherman and Serfling, 1961). It is possible to calculate in the U.K. also that excess mortality is considerable in many years even in the absence of a major epidemic, and that much of the excess is among those aged 65 years or more (Table 7). The number of persons 65 years of age and over in England and Wales at the present time is approximately 6.75 million (Central Statistical Office, 1974). The average excess mortality in England and Wales in those 65 years of age and over in the winters 1964/5 to 1971/2 when influenza was present was approximately 19,000. If all the excess mortality were due to influenza, this would represent a mortality rate of about 0.3% in this age group. If

TABLE 7. Mortality in excess of that in non-influenza winters in England and Wales, all ages and 65 years and over

		1964/5*	1965/6*	1966/7	1967/8*	1968/9†	1969/70†	1970/71	1971/2†
Excess mortality	65 yrs								
1 September–	and over	3866	27,446	0	43,838	3037	18,836	0	15,552
31 May	All ages	9038	35,019	0	48,028	8796	26,319	0	16,097

\* Excess mortality 1964/5–1967/8 calculated in comparison with the influenza-free winter of 1966/7, and † 1968/9–1971/2 in comparison with 1970/71.

influenza vaccine were completely protective, one death might be prevented by the vaccination of about 330 elderly persons. However, it is unlikely either that all the excess mortality is due to influenza, or that vaccine will prevent all influenza deaths. Nevertheless, a vaccination programme which even approaches an effect on mortality of this order, and which should in addition prevent much illness, deserves serious consideration.

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