SECTION 6

PLANNING FOR THE NEXT PANDEMIC

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Planning for influenza epidemics

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Summary

In the present circumstances, influenza vaccination cannot produce a significant reduction in the incidence of the disease without preliminary preparation and planning. The epidemiological situation is constantly changing, and vaccines should be chosen for their suitability for prevailing conditions. When viral antigens undergo appreciable change, and immunity in the population is low, people are especially susceptible to infection with live vaccines made from the new variants. Because of their potential high yield, it is therefore possible at this time to consider the use of these vaccines on a large scale. In interpandemic years, killed vaccines should be used selectively for the protection of individuals, but may also be considered for more general use in closed communities. Vaccines should as far as possible contain the same antigens as the epidemic virus. Reassessment of the influenza situation should be made annually, taking into account the types of viruses in circulation, the immune state of the population and any other factors likely to affect influenza outbreaks. Regular attempts to do this would ultimately improve the standard of forecasting.

Random immunization, as is practised for other virus diseases, is unprofitable in influenza.

Introduction

Few human epidemic diseases cannot now be controlled or eradicated by appropriate hygiene measures and by vaccination. Influenza therefore remains as the ultimate challenge, because not only is the natural history of the disease still obscure but, in spite of the production of many excellent vaccines, there is no record of any major epidemic having been halted or appreciably reduced by medical

intervention. It does therefore seem that there has been some failure of organization, and of the application of the discoveries of science to the control of the disease. Smith (1974) found that regular use of a commercial influenza vaccine on an unselective basis did not reduce sickness absence in a large number of Post Office employees in 2 successive years. It is suggested that such a finding was inevitable especially at a time when antigenic drift was in progress, and that with some preliminary planning it would be possible to use vaccination more profitably. In the following paragraphs, the factors of importance in the use of influenza vaccine will be considered and some of the author's own experiences in the Hong Kong (H₂N₂) subtype period which might give an indication of how to formulate a suitable strategy.

Types of influenza vaccine

Parenteral killed vaccines generally protect against a homologous strain for about 1 year. As the antigenic composition of the vaccine and epidemic viruses diverge, however, protection is reduced until it is finally abolished by a major subtype change. The crux of the influenza vaccination problem is therefore that, at the time the demand for vaccine is greatest, the vaccine itself is least plentiful. Hence, vaccination policy in the past has concentrated on the protection of the old and chronically sick and has made little conscious attempt to prevent the spread of the disease other than in closed communities such as boarding schools, nurses' homes and barracks. Much effort has been devoted to the improvement of killed vaccines which are available in a number of different forms. In general, they seem to be better suited to the boosting of antibodies

against viruses with which the individual has been antigenically primed than in creating antibody against a wholly new variant. It seems likely that when experimental and safety problems have been solved adjuvant vaccines will be especially useful because they induce very high titres of antibody, which should last longer and have a wider antiviral spectrum than those induced by conventional preparations.

Live vaccines which have now been experimented with for a considerable time appear to have properties which could do something to repair the deficiencies of killed vaccines. Their protective capacity depends on their ability to produce active infections and appropriate antibody rises. Since they consist only of crude virus-infected allantoic fluid, they can be grown very rapidly from a suitable strain and the yield is sufficiently high to enable us to think about mass vaccination. Greater forethought is necessary before prescribing their use than is necessary with killed vaccines, but logically it would seem that they could be most profitably used when a new virus variant has arisen and everybody is antibody-free.

Laboratory criteria for protection against influenza

The data about to be presented will be based solely on crude circulating haemagglutination-inhibiting (HI) antibody as an index of protection. Although immune mechanisms against influenza are undoubtedly mediated by many factors (Beare *et al.*, 1968; Beare and Bynoe, 1969), there is also no doubt that the old-fashioned HI test provides a valid criterion of resistance to infection (Hobson, Beare and Gardner, 1971). Hobson and colleagues showed that in a series of trials in Salisbury in which a 1965 influenza B virus was used, 55% of those free of HI antibody became infected, and that there was a regular inverse relationship between initial HI titres and susceptibility to infection (Fig. 1). A basically similar pattern was obtained with influenza A viruses (Fig. 1), except that the infection rate in those who were antibody-free was much higher. The precise reason for this is not known but it seems possible that many of those who had apparently had no HI antibodies to the influenza B virus had in the past been infected with antigenically related strains, whereas in the case of influenza A viruses in which antigenic drift is punctuated by major antigenic changes, susceptibility is more complete in the early years of a new subtype period.

Epidemiology of the H₃N₂ subtype in Great Britain

The expected invasion of the country by the Hong Kong virus occurred in the winter of 1968–1969. There was no sudden epidemic, but a slow, insidious spread of the virus which produced little morbidity and many inapparent infections. When the influenza

FIG. 1. The infection rate of volunteers challenged with various influenza viruses in relation to their pre-challenge titres of homologous serum HI antibody (Hobson *et al.*, 1971).

outbreak finally died down in the early summer of 1969, about one-third of the population had acquired HI antibody. It is thought that the spread of the virus had been slowed by residual anti-neuraminidase antibodies to the 1967 Asian strain in which the neuraminidase had been the same as that of A/Hong Kong/68. The following winter (December 1969–January 1970), a truly explosive outbreak of Hong Kong influenza took place which occupied few weeks only and then suddenly subsided. Following that outbreak, two-thirds of the population had HI antibody, and the interpandemic picture of antigenic drift followed by localized outbreaks of influenza has remained with us ever since.

Vaccination in the H₃N₂ era in Great Britain

Experiments with live and killed vaccines were being carried on in this country during the early years of the Hong Kong invasion, and while it is obviously not possible to draw too many inferences from the possible effects of the epidemiological situation on the conduct of these trials, a general description of our experiences may be useful. An inhibitor-resistant Hong Kong/68 virus was being given to volunteers in relatively low dosage in 1968–1969 (Beare and Bynoe, 1969), and some of the results are illustrated in Tables 1–3. Although the virus itself was not highly infective, this low dose managed to infect a high proportion of antibody-free volunteers. By the summer of 1969 when the Hong Kong strain had been circulating naturally for some time, it seemed possible that more resistance was being encountered. A field trial of live and killed Hong Kong vaccines was then planned for the

following winter based on a previous study of influenza B vaccines (Beare *et al.*, 1968). One hundred and fifty people would be recruited and allocated at random to three vaccine groups. One of these would receive live, attenuated Hong Kong vaccine by the intranasal route, one parenteral killed vaccine and the third group would function as a control and be given killed influenza B vaccine. Subsequently, they would all be challenged with live, partly attenuated Hong Kong virus and the infection rates in the vaccinated groups compared with that in the controls. Since a large outbreak of natural influenza ended shortly before the trial was due to commence, conditions were scarcely ideal for a trial of this kind.

TABLE 1. Inhibitor-resistant A/Hong Kong/68 (H₃N₂) live vaccines in antibody-free volunteers at the Common Cold Unit during the autumn and winter of 1968–1968. Virus dose was 10^{6.5} fifty per cent egg-infecting doses (EID₅₀)

Date of trial	Excretion of virus *	HI antibody rises *
October–November, 1968	6/7	7/7
January–February, 1969	5/7	6/7
March, 1969 (A)†	3/6	6/6
March, 1969 (B)†	3/7	5/7
March, 1969 (C)†	4/7	6/7

* In all tables, numerators are positive findings and denominators number of specimens tested.

† A, B and C signify inhibitor-resistant vaccines.

TABLE 2. Inhibitor-sensitive, low temperature-adapted live A/Hong Kong/68 vaccines in antibody-free volunteers at the Common Cold Unit

Date of trial	Excretion of virus	HI antibody rises
March 1969	4/10	8/9
March 1969	8/9	9/9

TABLE 3. A/Hong Kong/68 live vaccines in antibody-free volunteers at the Common Cold Unit during the summer of 1969

Date of trial	Type of vaccine	Virus dose (log EID ₅₀)	Excretion of virus	HI antibody rises
May–June, 1969	Inhibitor-resistant	5.5	4/7	4/7
May–June, 1969	Inhibitor-sensitive	5.5	5/6	6/6
June–July, 1969	Inhibitor-resistant	6.0	3/9	4/9
June–July, 1969	Inhibitor-sensitive	6.0	8/11	7/11

Nevertheless, such a hazard is commonplace in epidemiological trials of influenza vaccine, and our results may help to show how changing circumstances can affect the efficacy of influenza vaccine. The live vaccine, very similar to that used in Salisbury, produced little response (Fig. 2); the challenge virus, which was simply a different kind of live vaccine, immunized everybody with HI titres of 36 and below (Fig. 3) but had no effect on those with higher titres. The killed vaccine, however, induced antibody rises even in people with initial very high titres (Fig. 4) and seemed to be all the more effective because the people had been antigenically primed. Following the challenge, the infection rates in the live vaccine, killed vaccine and control groups were 13%, 8% and 38% respectively (not illustrated).

FIG. 2. A/Hong Kong/68 inhibitor-resistant live vaccine virus used in a field trial in January–March 1970. In Figs. 2–4 continuous diagonal lines denote lines of no significant antibody rises, and broken lines those of 4-fold rises or greater. Volunteers who were later considered to have been infected by the challenge virus (as judged by virus excretion, antibody rise or both) are encircled (Beare, A.S., Bradburne, P.D. and Gardner, A.W., unpublished data).

FIG. 3. A/Hong Kong/68 partly attenuated, inhibitor-sensitive challenge virus used in control group in the field trial of January–March 1970.

FIG. 4. Antibody rises following use of killed vaccine in the field trial of January–March, 1970. O, Infected by challenge.

Planned influenza vaccination

It is possible to make some sort of plans for recurring influenza epidemics which would be based on logical principles. No appreciable impact on pandemics can at present be visualized without the use of live vaccines. They alone can be prepared in sufficient quantity at short notice to provide for mass vaccination. It is never too late to vaccinate, but as a rule areas most distant from places in which new influenza A subtypes appear can depend on 6–12 months in which to prepare, test and use a vaccine of this kind. For perhaps 2–3 years large-scale vaccination with live virus could continue, and once antigenic drift had set in, selective use of killed vaccines based on regular assessment of the epidemiological situation would once again be instituted. In the present state of knowledge no more radical programme can be recommended. Ultimately, greater efforts would have to be made to improve the accuracy of forecasting influenza epidemics. Continued surveillance, accumulation of climatic data, repeated surveys of protective antibodies in the population, careful analysis of epidemic viruses and regular post-mortems on past failures would ultimately convert a gamble into something approaching a science.

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