Appendix C.—Summary of Medical Literature Review of Effectiveness of Inactivated Influenza Virus Vaccines*

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For purposes of analysis, vaccines were characterized by populations used for testing, type of vaccine, dose, number of doses, whether the vaccine was proven to be immunogenic, the interval between vaccination and challenge, whether the naturally *occurring* challenge was with homologous or heterologous virus, the clinical attack rate of illness in the population, and the calculated efficacy.

Seventy-seven trials reporting effectiveness against naturally occurring influenza were identified, 60 for type A and 17 for type B influenza. Three trials were rejected; in two of these, no protection was seen but the attack rate was low and influenza virus was not shown to be a cause of illness, and in one, protection was 23 percent but vaccine was given during the outbreak. Two of these were type A trials and one was a type B trial. Two type A and four type B trials were with adjuvenated vaccine, a type of vaccine never distributed for general use in this country. These were also excluded from this analysis.

The range of reported effectiveness for each virus type was O to 96 percent. The effectiveness for aqueous inactivated vaccines varied according to virus type and relationship of challenge virus to vaccine virus. A designation of homologous challenge indicates that vaccine virus and epidemic virus were identical, whereas heterologous indicates the natural challenge was with a virus that exhibited minor (drift) or major (shift) antigenic differences from vaccine virus. The majority of trials reported effectiveness greater than 60 percent for homologous virus challenge, but protection against heterologous virus was more variable. Only six trials in the elderly were reported and these were for type A. No trials involving infants and small children were identified.

Effectiveness was also summarized by population group and vaccine dose among those experiencing challenge with homologous virus. Greater protection was reported for studies involving military personnel than civilian, and this was most notable for type B vaccines. This may be partly explained by the fact that early trials involved the military primarily and higher doses of vaccine were used than in later trials. Two of the civilian trials with type B vaccine were in remote populations (South Pacific natives and Alaskan Eskimos) who experienced very high attack rates of illness; the vaccines failed to exhibit any protective effect. No studies in remote populations were identified for type A virus.

Only eight trials used two doses of vaccine, although three others involved persons who had received either one or two doses. No difference in protection occurring in these trials compared to those using one dose was noted. Immunogenicity of the vaccine was proven in the majority of trials. In one trial, the vaccine was proven not to be immunogenic, and this resulted in 13-percent protection of an elderly population against a heterologous virus. Clinical attack rates of illness in the population appeared unrelated to degree of effectiveness. Only four reports involved very high attack rates (70 to 90 percent), the two noted above for type B with no protection and two with type A in the military with reported effectiveness of 57 and 77 percent. Protection against antigenically novel viruses (shift) with homologous vaccine virus was generally low in 1947 and 1968 but good in 1957.

Protection 14 to 16 months after vaccination was O, 35, 80, and 85 percent in four studies and 60 percent after 3 years in one study. All other studies involved challenge in 1 to 9 months after vaccination.

Thus, factors evaluated that might relate to degree of effectiveness of vaccine were remoteness of population studied, attack rates of illness and age and health status of given populations, dose of vaccine (particularly for type B), interval between vaccination and challenge, and antigenic novelty of the virus. Any one or more of these factors may be more important for one type of vaccine than for another, but the relative significance of each could not be discerned. Clearly, the most significant factor identified in this review that influences degree of effectiveness is the antigenic relationship between the vaccine and challenge (epidemic) virus.

● NOTE This report was presented at a Workshop on Influenza B Viruses and Reye's Syndrome, National Institute of Allergy and Infectious Diseases, **National Institutes of Health, Bethesda,** Md., July 30-31, 1979. It is based on a search of the English language literature, **Eighty-five percent of possible references identified were obtained. Sources** used were as follows: C G Loosli, International ***Bibliography of Influenza,*** 1930-1959; Medlars Service **of the National Library Medicine;** and *Cumulative Index Medicus.* The author's bibliography appears a t the end of this appendix.

Conclusion: Review of the medical literature on effectiveness of aqueous inactivated influenza virus vaccines provided support for the belief that these vaccines are generally effective for prevention of clinical influenza, particularly if the epidemic virus is antigenically similar to the vaccine virus and if vaccine is given in the immediate few months preceding exposure. The commonly quoted figure of 70-percent protection against illness in this circumstance seems reasonable. Deficiencies in present knowledge exist regarding effectiveness of aqueous vaccines in elderly and chronically ill persons, on duration of effectiveness, on the mechanism of protection, and on type B vaccines in general.

Appendix C Bibliography*

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