

Appendix B.—Safety and Efficacy of Inactivated Influenza Vaccine

Description of Inactivated Influenza Virus Vaccine

Influenza vaccines can be categorized in two basic groups—live, which contain small amounts of live, attenuated (weakened) influenza viruses, and *inactivated*, which contain either whole influenza viruses or subunits of viruses. Only inactivated influenza viruses are licensed for general use in the United States; therefore, this discussion of vaccine safety and efficacy pertains exclusively to inactivated vaccines.

Inactivated influenza virus vaccines have been manufactured and used in the United States since the 1940's (64). Early development of influenza vaccines was spearheaded by the Armed Forces Epidemiological Board and its Commission on Influenza (12). The early vaccines have undergone several improvements.

Influenza virus vaccine production procedures have been described elsewhere (33,71).

Today, there are two types of inactivated influenza virus vaccine commercially available in the United States, whole virus and subunit. The antigenicity of whole virus vaccine has been demonstrated more extensively than that of subunit vaccines (91). On the basis of evidence generated from clinical trials conducted in 1976, however, subunit vaccines are now considered by some researchers to be equally antigenic with whole virus vaccines in adults with prior influenza virus antibody production and less antigenic in either children or adults with no prior influenza virus antibody production (51). In some studies, administration of a booster injection of subunit vaccine yielded antibody levels comparable to those produced by whole virus vaccines (21,44). In other studies, however, a second injection yielded no "booster" effect among those responding poorly to an initial injection (25). Subunit influenza vaccines tend to cause fewer adverse reactions than whole virus vaccines (30,51,65).

Vaccine Efficacy

There are two major types of investigations used to evaluate the efficacy of influenza vaccines. First, clinical trials—in which vaccinated subjects are exposed, either by design or by chance, to influenza organisms—can be used to determine a vaccine's protective efficacy. Second, antibody response studies—in which prevaccination and postvaccination serum antibody levels are measured in vaccinated

subjects—are used to determine the capacity of a vaccine to induce antibody information. It can be difficult to conduct clinical trials involving influenza vaccine, because the occurrence of influenza epidemics caused by specific strains of viruses is often difficult to predict, and because intentional exposure of subjects raises ethical concerns. Antibody response studies by themselves are not usually relied on to assess a vaccine's efficacy; rather, they provide data from which efficacy or protection be inferred. Often, data from antibody studies are obtained from vaccinated subjects not subsequently exposed to influenza virus; therefore, achievement of a certain postvaccination serum antibody level, for example, a fourfold increase over prevaccination level, is sometimes used to help assess a vaccine's clinical efficacy. Antibody responses can also be described in terms of the percentage of a vaccinated population with postvaccination antibody levels $\geq 1:40$. Some clinical experiences document a correlation between a particular level of serum antibody rise and clinical efficacy. A few of these experiences are discussed briefly below. Others have been described previously (23,44,95).

Numerous factors affect a vaccinated person's antibody response to an inactivated influenza vaccine, and thus affect a vaccine's effectiveness. First, and obviously, the vaccine's potency (amount of antigen), purity (freedom from contaminating material), and other measures of quality are important. Second, the degree to which the antigenic components of the virus(es) in a vaccine match the antigenic components of the virus(es) circulating in the environment greatly affects the effectiveness of the vaccine (see app. C). Third, a vaccinated person's antibody response to a given vaccination is influenced by his or her prior exposures to influenza viruses either through vaccination or acquisition of disease (natural immunity) (21,29,36,49). Fourth, the duration of immunity conferred by influenza vaccination tends to be short (i.e., usually 1 year, possibly 3 years, and perhaps longer); further, the duration of immunity varies substantially with age and other host factors.

Usually, inactivated influenza vaccines contain either whole cells or antigenic subunits (neuraminidase and hemagglutinin) from two or more strains of influenza viruses. Ever since 1943, in the United States, vaccines have been marketed with at least one type of influenza A virus and one type of influenza B virus. In recent years, trivalent vaccines, containing

two types of influenza A viruses and one type of influenza B virus, have been marketed. Much more data are available concerning the safety and efficacy of influenza A virus vaccines than influenza B virus vaccines.

The type(s) of influenza virus(es) (e.g., type A or B) that circulate in the United States can easily change, sometimes from year to year (27). Furthermore, even in subtypes within a particular type of virus (e.g., H3N2 or H1N1 type A influenza viruses), the antigenic components can change in a fashion that alters the virus's susceptibility to a person's antibodies. Because the manufacturing and distribution processes for influenza vaccine take from 6 to 9 months, the type(s) of influenza virus selected to be represented in a vaccine for a given year may not be in circulation at the time the vaccine is actually used. As a result, in a given year, the vaccine being administered may not stimulate antibodies to—and therefore not help protect against—the type(s) of influenza virus(es) producing disease. Evidence of the protective efficacy of a current vaccine formulation is therefore often difficult or sometimes impossible to obtain before a vaccine is released by the Bureau of Biologics for general use. There can be, however, some degree of overlapping protection among different types of influenza viruses (70,118).

Clinical Studies

The clinical efficacy of inactivated influenza vaccines has been debated virtually since their development in the 1940's. Clinical studies have yielded clinical efficacy rates ranging from 0 to 90 percent (104). (Note: The clinical efficacy rate refers to the percentage decline in the incidence of clinical influenza among a group of vaccinated subjects as compared to the incidence of clinical influenza among a group of unvaccinated subjects.)

The following studies are used to illustrate clinical efficacy rates for inactivated influenza A virus vaccines:

1. Ferry, et al., in Australia conducted three clinical trials of a trivalent subunit influenza vaccine containing 250 international units (IU) of A/Victoria/3/75 virus, 250 IU of A/Scotland/840/74 virus, and 300 IU of B/Hong Kong/8/73 virus (36). The first trial involved 698 vaccinees and 2,034 unvaccinated controls; all subjects were members of a hospital staff. Although the difference in the incidence of respiratory tract infection (RTI) between the two groups was not significant, the incidence of influenza (diagnosed on the basis of clinical and serological determinations) was 81 percent lower among vaccinees.

In the second trial, the same vaccine was administered to 480 laboratory workers; another 583 laboratory workers in the same institution served as controls. There were no statistically significant differences in either incidence of RTI (47 cases among vaccinees v. 51 cases among controls) or isolation of influenza viruses (24 isolates among vaccinees v. 24 controls) between the two groups. However, the vaccinated group lost only 493 days of work compared to 837 days for the unvaccinated. The differences in work loss between the two groups might be attributable to a less severe type of influenza among the vaccinated.

In the third trial, involving patients in a geriatric home, 154 vaccinated volunteers were compared with 63 unvaccinated controls. There was no statistically significant difference in the incidence of influenza between the two groups, but the severity of influenza cases was deemed by the investigators to be less in the vaccinated group.

The authors attributed the difference in vaccine efficacy in these three trials to possibly differences in prevaccination antibody levels; those with lower prevaccination antibody levels and those being vaccinated for the first time experienced less postvaccination influenza.

2. Hoskins, et al., in England studied the protective efficacy of inactivated influenza vaccines among 375 school boys who experienced three epidemics: 1972 (A/England/42/72), 1974 (A/Port Chalmers), and 1976 (A/Victoria) (49). During the three epidemics collectively, the cumulative case-rates were approximately the same (i.e., 40 to 50 percent) among all boys, regardless of their vaccination status. Those boys who were vaccinated before each epidemic experienced influenza at the same rate as those who received no vaccine at all when evaluated retrospectively over the three epidemics. Boys vaccinated for the first time were partially protected against the strain of influenza causing the next outbreak.

In 1976, the year A/Port Chalmers virus caused the influenza outbreak, the attack rate among boys who received no relevant vaccination was similar to that among boys who received A/Port Chalmers vaccine that year and who in addition had been vaccinated against other strains in earlier years. Boys vaccinated with A/Port Chalmers that year only (with no prior influenza history) experienced a substantially lower attack rate. Also in 1976, immunity derived from natural infection (A/Port Chalmers/1974 or A/England/1972) appeared

to provide better protection than did any vaccination.

Hoskins concluded that "when a new antigen subtype, e.g., A/Port Chalmers, first appears and a population is completely susceptible, a vaccine will have its maximum effect and may be expected to protect 50 percent or more of those vaccinated However, this benefit is short-lived. As a strain undergoes antigenic drift, subjects previously protected from natural infection by vaccination will be at risk and cannot be effectively protected by further vaccination with either the same or a later strain. " On the basis of his findings, Hoskins questioned the effectiveness and wisdom of annual influenza vaccination within a population.

3. Sparks, in another English school, reported findings similar to those of Hoskins' (117). He claimed that influenza vaccination only postpones an attack and that transient protection provided by vaccination can prevent the development of the long-term immunity resulting from an attack of influenza.
4. During the 1977-78 influenza season, Couch and coworkers in Houston, Tex., compared the clinical protective efficacy of two successive annual influenza vaccinations among 129 elderly subjects (51 to 78 years old; median, 65 years) (21). In 1976, all subjects received bivalent influenza vaccine containing A/Victoria/75 (H3N2) and A/New Jersey/76 (Hsw1N1) antigens. In October 1977, 74 of those subjects received another bivalent vaccine containing A/Victoria/75 and B/Hong Kong/72 antigens. Vaccinees voluntarily submitted information about their history of respiratory illnesses, which were classified according to severity. Vaccinated subjects' sera samples were also analyzed for antibody content. Among the 74 subjects who received the second vaccination, there was no statistically significant reduction on the incidence of mild illness, but there was a 60-percent reduction in severe illness.
5. At the Surgeon General's Meeting on Influenza Immunization held on January 22, 1980, several vaccine efficacy studies were reviewed (104). In one of these studies, 169 college students in Atlanta, Ga., were given 2 doses of a vaccine containing an A/U.S.S.R.-like (H1N1) antigen and 181 students were given a placebo vaccine. An epidemic of A/Brazil/78-like (H1N1) influenza followed in Atlanta 7 to 10 weeks after the students were vaccinated. The use of this vaccine in this study reduced the incidence rate

of laboratory-confirmed influenza illness by nearly 50 percent.

Reviews of influenza vaccine safety and efficacy are contained in the written summaries of conferences on influenza sponsored by the Department of Health and Human Services between 1977 and 1980 (97-104).

Vaccine Efficacy During Years of Inexact Antigenic Match Between Vaccine Virus(es) and Circulating Virus(es)

As described in appendix A, influenza viruses sometimes change their chemical makeup from season to season and even within a single season. Small changes—i.e., those within a given type of virus such as H3N2 influenza A virus—are collectively referred to as "antigenic drift. " Larger changes—such as a replacement of an H3N2 influenza A virus by an H1N1 influenza A virus—are called "antigenic shifts. "

During the 8-year period from 1970-71 through 1977-78, there were four episodes of antigenic drift in the predominate H3N2 influenza A virus circulating in the United States. These drifts occurred in **1972-73** (Hong Kong to England), **1973-74** (England to Port Chalmers), 1975-76 (Port Chalmers to Victoria), and 1977-78 (Victoria to Texas).

The degree to which antigenic drift affects the effectiveness of a given H3N2 influenza A virus vaccine creates yearly public debates (97-104). Because antigenic drift can occur within the 6 to 9 months between vaccine formulation and vaccine distribution, in some years the influenza A virus contained in the distributed vaccine somewhat differed antigenically from the circulating viruses causing disease. In three clinical trials (70,85, 118) and one retrospective epidemiologic investigation (8), researchers have attempted to assess the clinical effectiveness of vaccines containing an H3N2 virus that differed from the predominant circulating H3N2 virus causing disease in a distinct geographical location.

Clinical Evidence.—In 1977, Meiklejohn and coworkers assessed the efficacy of a trivalent inactivated influenza vaccine (**400 chick cell agglutinating (CCA) units of A/Victoria/3/75, 400 CCA units of A/New Jersey/76 and 500 CCA units of B/Hong Kong/72 viruses**) against a variant of A/Victoria virus (A/Texas/1 /77-like virus) among military personnel in Colorado (70). In November 1976, approximately 4,200 military students at Lowry Air Force Base (AFB) were given this vaccine; subsequently, this population was continually altered by the arrival of approximately 200 new students and the departure

of a similar number of students each week. The newly arrived students intermingled extensively with the remaining ones. An influenza outbreak (caused by an A/Texas/1/77-like virus) occurred at Lowry AFB in February 1977, causing 87 cases of influenza. During the first and second weeks of the outbreak, the attack rates among the unvaccinated students were 20.0 and 23.6 cases per 1,000 persons per week, and the attack rate among the vaccinated never exceeded 2.3 cases per 1,000 persons per week. For the remaining 3 weeks of the outbreak, attack rates were 1.4, 4.7, and 1.2 cases per 1,000 among the unvaccinated and 2.2, 2.3, and 1.2 among the vaccinated. The investigators, using three different methods of calculation, estimated the clinical efficacy rate of the vaccine to range from 69.0 to 83.1 percent.

During the winter of 1974-75, CDC conducted among university students an open field trial of vaccines containing either inactivated or live influenza A/England/42/72 (H3N2) virus (85). Influenza A/Port Chalmers/1/73 (H3N2) which differed antigenically from A/England/42/72, however, was the predominant H3N2 influenza virus causing disease among volunteer participants in this study. The influenza attack rate among placebo recipients (unvaccinated control group) was 69 cases per 1,000 persons, whereas the attack rate among inactivated vaccine recipients was 25 cases per 1,000 persons, and 36 cases per 1,000 persons among live vaccine recipients. Using the following formula, OTA calculated the clinical effectiveness rate of the inactivated influenza vaccine during this trial to be 64 percent (I):

Vaccine effectiveness =

$$\frac{(\text{attack rate in unvaccinated group} - \text{attack rate in vaccinated group}) \times 100}{\text{attack rate in unvaccinated group}} \%$$

Retrospective Epidemiologic Investigation.—In 1972, Stiver and associates studied the clinical effectiveness of a vaccine containing Hong Kong influenza virus antigen (A2Aichi/2/68) during an outbreak of A2England/72 influenza among air force recruits in Colorado (118). Among 979 vaccinees, the influenza attack rate was 18.4 cases per 1,000 persons. Among 2,955 unvaccinated subjects, the influenza attack rate was 46.0 cases per 1,000 persons. The vaccine's clinical effectiveness rate was calculated to be 60 percent ($p < 0.01$ by chi-square test).

Barker and Mullooly attempted to assess the impact of the A/Hong Kong/68 (H3N2) influenza virus vaccine on the rates of pneumonia-influenza associated hospitalization and mortality among a defined population 65 years and older at Kaiser-Permanente Hospital in Portland, Oreg., during the 1972-73 epidemic caused by A/England/42/72 (H3N2) influenza virus (8). These researchers retrospectively re-

viewed the medical records of a 5-percent sample of Kaiser-Permanente patients 65 years and older. Prior to this epidemic, 20 to 30 percent of the chronically ill elderly Kaiser-Permanente patient population was vaccinated; vaccinees and nonvaccinees were comparable in age and distribution of chronic disease. Among those vaccinated, there was a 72 percent reduction in hospitalizations associated with pneumonia or influenza during the 1972-73 influenza epidemic. Further, no deaths were recorded among the vaccinated, while death rates among the unvaccinated were 6 out of 10,000 non-high-risk individuals and 35 out of 10,000 high-risk individuals.

These researchers conducted a similar analysis of the impact of the A/Taiwan/1/64 (H2N2) virus (8). There were no statistically significant differences in either hospitalization or mortality rates between the vaccinated and unvaccinated groups. The authors attributed the lack of vaccine impact during the 1968-69 epidemic to the major shift from an H2N2 to an H3N2 antigenic configuration in the circulating virus.

On the basis of the findings of these three clinical trials and one epidemiologic investigation, OTA assumed that the clinical effectiveness rate of the inactivated influenza virus vaccines used in three years involving antigenic drift of H3N2 virus (i. e., 1972-73, 1974-75, and 1977-78) was at least 60 percent.

Antibody Response to Influenza Vaccine Among Specialized Populations

The following studies illustrate variations in antibody response to influenza vaccine among selected subpopulations who are likely to receive influenza vaccine. Several studies of influenza vaccines in special populations were published previously in the December 1977 (supplement) issue of the *Journal of Infectious Diseases*.

Neoplastic Diseases.—Shild and coworkers demonstrated an adequate antibody response to a trivalent influenza vaccine (A/New Jersey 1976 (Hsw1N1), B/Hong Kong/5/72, and A/Victoria/3/75 (H3N2)) among 36 patients with solid tumors and a less-than-favorable response in 46 patients with lymphomas (110).

Ganz, et al., demonstrated a fourfold rise in antibody titers to a bivalent influenza vaccine (A/New Jersey /76(Hsw1N1) and A/Victoria/ 75(H3N2)) in 41 to 47 percent of 17 patients with various types of cancer and on various types of chemotherapy (40). Orbals, et al., found that 71 percent of 42 cancer patients (21 with lymphoreticular neoplasms and 21 with solid tumors) demonstrated a fourfold or greater increase in serum antibody titers to A/New

Jersey/1976 influenza vaccine as compared to 91 percent of control subjects (92). Also, immunization at the time of chemotherapy administration lowered the incidence of seroconversion from 93 percent to 50 percent.

Silver and Weinerman administered a bivalent influenza vaccine (A/Port Chalmers/1/73 (H3N2) and B/Hong Kong/5/72) to 44 patients with cancer and 27 healthy controls (115). Against the A antigen, 16 of the cancer patients and 25 of the controls yielded a fourfold or greater increase in antibody titer. Against the B antigen, 14 of the cancer patients and 20 of the controls yielded a fourfold increase in serum antibodies. Nineteen of the cancer patients had lymphomas, and only four of these patients demonstrated a fourfold increase in antibody level.

Neoplasms in Children.—In 1978, Douglas and associates gave one or more of the following antigens to 54 children with malignancies: A/U.S.S.R./77 (H1N1), A/Texas/77 (H3N2), and B/Hong Kong/72 (25). By the end of the study, the percent of subjects who developed a serum influenza antibody titer ≥ 40 (indicative of a good antibody response) was as follows:

- 49 percent of those given A/U.S.S.R./77 vaccine,
- 59 percent of those given A/Texas/77 vaccine, and
- 24 percent of those given B/Hong Kong/72 vaccine

Systemic Lupus Erythematosus.—Ristow, et al., found a fourfold or greater antibody response to A/New Jersey/76 (Hsw1N1) vaccine in 14 of 29 patients with systemic lupus erythematosus, compared to 18 out of 29 control subjects (109).

Herron, et al., studied the safety and efficacy of an influenza vaccine (A/New Jersey/76 and A/Victoria/75) among 62 patients with rheumatic diseases, including systemic erythematosus, rheumatoid arthritis, and degenerative joint disease and among 32 healthy control subjects (46). Among the patients with rheumatic diseases, 62 to 87 percent seroconverted to A/New Jersey/76 and 62 percent seroconverted to A/Victoria/75. Thirteen of the rheumatic disease patients experienced a flare up of their disease.

Tecson and Bornstein have cautioned against repeated yearly influenza vaccination because of potential complications (121).

Pregnancy.—Sumaya and Gibbs administered A/New Jersey/76 influenza vaccine to 56 pregnant women and found no significant difference in the antibody responses between pregnant and nonpregnant adults (120). Further, no significant immediate

maternal reactions or increased fetal complications were observed.

Murray and associates studied the antibody responses to A/New Jersey/8/76 (Hsw1N1), A/Japan/305/57 (H2N2), and A/Hong Kong/8/68 (H3N2) influenza vaccine in 59 pregnant and 27 nonpregnant women (77). There were no significant differences in antibody responses between pregnant and nonpregnant subjects.

Geriatric Population.—Serie and coworkers administered a trivalent influenza vaccine (A/Pasteur P 24.R (H3N2), A/Port Chalmers/73 (H3N2) and B/Hong Kong/73)) to 523 geriatric hospitalized patients with an average age of 83 years (113). Serologic and virologic investigations were performed in 110 patients. The incidence of clinical influenza caused by type A/Victoria was roughly twice as high among the unvaccinated as that among the vaccinated. The mortality rate among all vaccinees was 0.19 percent compared to 3.90 percent of those unvaccinated. When 80 percent of patients in a particular hospital section was immunized, the incidence of influenza was reduced by as much as three times.

Howells and associates have also assessed the value of this vaccine among the elderly (so).

Multiple Sclerosis.—Banford, et al., administered a bivalent influenza vaccine (A/New Jersey and A/Victoria) to 65 patients with multiple sclerosis and compared the incidence of adverse neurological conditions among vaccinees with that among 62 unvaccinated control multiple sclerosis patients (7). Sixty-one of the vaccinated patients tolerated the vaccine well, and four developed new neurological complications. Among the 62 unvaccinated control patients, four also developed new neurological symptoms. The authors concluded that influenza vaccine posed no excessive risk of neurological symptoms among multiple sclerosis patients. Vaccine efficacy was not evaluated in this study.

Chronic Renal Failure, Renal Dialysis, and Transplant Populations.—McMillen and associates administered a bivalent influenza vaccine (A/New Jersey/76 and A/Victoria/75 by Wyeth Laboratories) to 23 chronic dialysis patients (age 30 to 72 years), 18 renal transplant patients (age 18 to 64 years), and 10 pediatric patients (6 on chronic dialysis and 4 with renal transplants) (68). Seroconversion was observed in 67 percent of all 29 dialysis patients and in 50 percent of all 22 renal transplant patients. Among the transplant group, patients 18 to 25 years old had a much lower seroconversion response (12.5 percent) than either those under 18 (75 percent) or over 25 (90 percent).

Osanloo and coworkers administered a bivalent

influenza vaccine (A/Victoria/75 and A/New Jersey/76) to 10 azotemic, undialyzed males, 19 hemodialyzed males, and 17 control subjects (93). Fifty-four percent of the control subjects, 53 percent of the hemodialysis patients, and 60 percent of the azotemic patients developed a fourfold greater increase in antibody levels to A/Victoria antigen. Against the A/New Jersey antigen, 92 percent of the controls, 89 percent of the dialyzed patients, and 90 percent of the azotemic patients developed a fourfold or greater rise in serum antibody levels. The authors noted that severe azotemia and/or immunosuppressive or corticosteroid therapy may depress certain antibody responses.

Vaccine Safety

The safety of influenza vaccine, like that of all vaccines, is evaluated on the basis of the incidence of adverse reactions to the vaccine that: 1) investigators in clinical trials report, or 2) practicing health professionals voluntarily report to CDC, FDA, or the vaccine manufacturer (86). Adverse reactions to vaccines can be classified as follows:

- **Local Reactions:** These reactions include pain, redness, and swelling at the vaccine injection site. Such reactions occur commonly, do not involve other areas of the body, and are usually minor and self-limiting.
- **Systemic Reactions:** These reactions include perturbations in one or more organ systems and can affect one or more areas of the body. Such reactions range from fevers to allergic reactions; their severity can be mild and short-lived, severe and long-lasting, or sometimes even fatal.

A recent study commissioned by the Department of Health and Human Services (DHHS) describes in detail the clinical and economic profiles of several selected types of adverse reactions to commonly used vaccines (4).

The safety of influenza vaccines became quite topical during the National Influenza Immunization Program of 1976, the so-called swine flu program. Unexpectedly, approximately 1 out of every 100,000 persons who received swine flu vaccine (A/New Jersey/76 Hsw1N1 virus) developed Guillain-Barre Syndrome (GBS), a neurological disorder that results in varying degrees of disability, ranging from temporary paralysis of extremities (arms and legs) to death (112). The relationship between influenza vaccines and GBS has received much publicity and the safety of influenza vaccines has been studied extensively during the past 4 years. The following descriptions of

each type of adverse reaction associated with influenza vaccine are based largely on such studies.

During the 1976-77 influenza immunization program, CDC coordinated a nationwide surveillance program to detect adverse reactions following influenza vaccination. CDC received a total of 4,733 voluntarily submitted reports of such reactions, including reports of 233 deaths, for the estimated 48 million persons vaccinated against influenza during the season (107). This surveillance program was the early warning system that led to the discovery of an association between GBS and influenza vaccination. Limitations to data collected in this system, however, are noted by CDC investigators (107):

Reports of illness that depend on voluntary reporting during a time of varying publicity are inappropriate for retrospectively developing rates of illness in a target population. . . . The passively reported data gathered through this surveillance system are of such a nature that they cannot be compared with data gathered from monitored defined populations.

According to a 1979 survey conducted by Opinion Research Corp. for the Bureau of Health Education, CDC, approximately 13 percent of all children and 5 percent of all adults receiving influenza vaccine in 1978 had an adverse reaction that resulted in a visit to a doctor, hospital, or clinic (123).

Local Reactions

Noble and associates investigated among University of Georgia students the safety and efficacy of two trivalent inactivated influenza virus vaccines (both the vaccines contained 7 micrograms of hemagglutinin from A/Texas/1/77 (H3N2) and from A/Brazil/11/78 (H1N1) viruses. One vaccine (Vaccine No. 1) also contained 7 micrograms of B/Hong Kong/8/73 while the other (Vaccine No. 2) contained 50 micrograms of B/Hong Kong/8/73 (104). The vaccine with 7 micrograms of each virus (Vaccine No. 1) was administered to 394 volunteers. The vaccine with 50 micrograms of B/Hong Kong/8/73 virus (Vaccine No. 2) was given to another 386 subjects. A placebo vaccine was given to another 396 volunteers. About 20 percent of those subjects receiving Vaccine No. 1 and 36 percent of those receiving Vaccine No. 2 developed sore arms at the vaccination site.

Eastwood and associates studied the reactions of 49 children (aged 4 to 11 years) to a surface-antigen-absorbed influenza virus vaccine containing 8.4 micrograms HA (hemagglutinin) of A/Victoria/3/75 (H3N2) and 12.7 micrograms HA of B/Hong Kong/8/73 per dose (30). Eighteen (37 percent) of the vaccinees experienced mild local reactions (slight soreness and aching at the inoculation site) during the 3

days following immunization. Two children (4 percent) also had local swelling, two had redness, and one developed a bruise.

Systemic Reactions

Systemic reactions to influenza vaccine can be classified as follows (1):

- *minor* (fever, malaise, myalgia [muscle aches])—all such reactions usually subside within 48 hours);
- *immediate—presumably allergic—responses* (breathing difficulties, certain skin eruptions, rarely severe allergic reactions [anaphylaxis]);
- *Guillain-Barre Syndrome (GBS)* (a paralytic disorder that usually starts in a person's extremities and moves up the body; approximately 50 percent of the cases recover completely within 1 year; 10 percent result in moderate to severe permanent disability; and 5 percent die); and
- *miscellaneous.*

1. *Minor:* In the study cited above, Noble and associates found a 2-percent incidence of fever ($>100^{\circ}$ F), a 5-percent incidence of malaise and myalgia, and a 6-percent incidence of headache among those subjects receiving Vaccine No. 2. Vomiting occurred in 6 recipients of Vaccine No. 2 (104).

Dr. William S. Jordan from the National Institute of Allergy and Infectious Diseases (NIAID) prepared an analysis of clinical trials involving the administration of inactivated influenza vaccine containing the A/U.S.S.R./77 (H1N1) antigen to approximately 2,000 subjects (100). Among nearly 1,000 subjects 13 years of age or older given two doses of either split or whole virus vaccine, only 18 developed fever ($> 100^{\circ}$ F). Twelve (36 percent) out of 33 subjects under 13 years old who received a placebo vaccine, however, also developed fevers.

In Eastwood's study cited above, one diabetic child experienced raised levels of urinary sugar and ketones which subsided in 2 days. No fevers were reported (30).

Dolin, et al., administered inactivated influenza A/New Jersey/76 virus vaccine in doses of 200, 400 or 800 CCA units to 199 adult health volunteers (23). All fevers subsided within 48 hours. Malaise—usually gone in 48 hours—occurred in 50 to 60 percent of vaccinees receiving 400 to 800 CCA units. Headache persisted beyond 48 hours in 9 to 19 percent of vaccinees.

Parkman, et al., summarized adverse reactions data from clinical trials involving 3,900 adults who in 1976 received various doses of A/New Jersey/76, A/Victoria/75, and B/Hong Kong/72 influenza virus vaccines (95). At doses below 800 CCA units, mild fever ($<100^{\circ}$ F) occurred in 0.6 to 12.8 percent of vaccinees. About 3.7 percent of recipients of a vaccine containing 800 CCA units developed fevers of 102° F.

2. *Immediate Reactions:* According to Dr. Kenneth McIntosh, University of Colorado, the incidence rate of severe allergic reactions (anaphylaxis) to influenza vaccine is 1 case per 4 million vaccinees (100).

Gross, et al., reported a case of meningoencephalitic syndrome following influenza vaccination in a 60-year-old woman allergic to chicken meat and eggs (45).

Horowitz reported a case of urticaria occurring in an n-year-old girl with asthma (48).

In the studies summarized by Parkman, et al., 2 of the 3,900 vaccinees experienced allergic reactions and both survived with no sequelae (95).

3. *Guillain-Barre Syndrome:* (See app. D.)

4. *Miscellaneous:* Perry and associates reported a case of reversible blindness from optic neuritis associated with influenza vaccination (96).