Immunization Safety Review: Influenza Vaccines and Neurological Complications EXECUTIVE SUMMARY

ABSTRACT

Infection with the influenza virus can have a serious effect on the health of people of all ages, although it is particularly worrisome for infants, the elderly, and people with underlying heart or lung problems. At least 35,000 people die in the United States every year from influenza infection. A vaccine exists (the "flu" shot) that can greatly decrease the impact of influenza. Because the strains of virus that are expected to cause serious illness and death are slightly different every year, the vaccine is also slightly different every year and it must be given every year, unlike other vaccines. The influenza vaccine that was used in 1976 for the expected "Swine Flu" epidemic (which never materialized) was associated with cases of a nervous system condition called Guillain-Barré syndrome (GBS). Ever since that time, public health leaders, doctors and nurses, and the public have wondered whether every year's influenza vaccine can cause GBS or other similar conditions.

The Immunization Safety Review committee reviewed the data on influenza vaccine and neurological conditions and concluded that the evidence favored acceptance of a causal relationship between the 1976 Swine Influenza vaccine and GBS in adults. The evidence about GBS for other years' influenza vaccines is not clear one way or the other (that is, the evidence is inadequate to accept or reject a causal relationship).

The committee concluded that the evidence favored rejection of a causal relationship between influenza vaccines and exacerbation of multiple sclerosis. For the other neurological conditions studied, the committee concluded the evidence about the effects of influenza vaccine is inadequate to accept or reject a causal relationship. The committee also reviewed theories on how the influenza vaccine could damage the nervous system. The evidence was at most weak that the vaccine could act in humans in ways that could lead to these neurological problems.

Immunization to protect children and adults from many infectious diseases is one of the greatest achievements of public health. Immunization is not without risks, however. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into day care, school, or college, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the evidence on possible causal associations between immunizations and cer-

tain adverse outcomes, and to then present conclusions and recommendations. The committee's mandate also includes assessing the broader societal significance of these immunization safety issues. While the committee members all share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group.

The committee reviews three immunization safety review topics each year, addressing one at a time. In this seventh report in the series, the committee examines the hypothesis that influenza vaccines are associated with an increased risk of neurological complications, particularly Guillain-Barré syndrome (GBS) and multiple sclerosis (MS).

The committee is charged with assessing both the scientific evidence regarding the hypotheses under review and the significance of the issues for society:

The *scientific* assessment has two components: an examination of the epidemiologic and clinical evidence regarding a possible *causal relationship* between exposure to the vaccine and the adverse event; and an examination of theory and experimental evidence from human or animal studies regarding biological *mechanisms* that might be relevant to the hypothesis.

The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event. Other considerations may include the perceived intensity of public or professional concern, or the feasibility of additional research to help resolve scientific uncertainty regarding causality.

The findings of the scientific and significance assessments provide the basis for the committee's recommendations regarding the public health response to the issues. In particular, the committee addresses needs for a review of immunization policy, for current and future research, and for effective communication strategies.

For its evaluation of the question concerning influenza vaccines and neurological complications, the committee held an open scientific meeting in March 2003 (see Appendix B) to hear presentations on issues germane to the topic. These presentations are available in electronic form (audio files and slides) on the project website (www.iom.edu/imsafety). In addition, the committee reviewed an extensive collection of material, primarily from the published, peer-reviewed scientific and medical literature. A list of the materials reviewed by the committee, including many items not cited in this report, can be found on the project's website.

THE FRAMEWORK FOR SCIENTIFIC ASSESSMENT

Causality

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by previous IOM committees (IOM, 1991; 1994a,b), convened under the congressional mandate of P.L. 99-660 to address questions of immunization safety. The categories of causal conclusions used by the committee are as follows:

1. No evidence
2. Evidence is inadequate to accept or reject a causal relationship
3. Evidence favors rejection of a causal relationship
4. Evidence favors acceptance of a causal relationship
5. Evidence establishes a causal relationship.

Assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The committee does not conclude that the vaccine does not cause the adverse event merely if the evidence is inadequate to support causality. Instead, it concludes that the "evidence is inadequate to accept or reject a causal relationship."

Biological Mechanisms

Evidence considered in the scientific assessment of biological mechanisms[1] includes human, animal, and *in vitro* studies related to biological or pathophysiological processes by which immunizations could cause an adverse event. When other evidence of causality is available, biological data add supportive evidence but they cannot prove causality on their own.

The committee has established three general categories of evidence on biological mechanisms:

1. *Theoretical.* A reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles, but it has not been demonstrated in whole or in part in humans or in animal models.
2. *Experimental.* A mechanism can be shown to operate in *in vitro* systems, animals, or humans. But, experimental evidence often describes mechanisms that represent only a portion of the pathological process required for expression of disease. Showing that multiple portions of a process operate in reasonable experimental models strengthens the case that the mechanisms could possibly result in disease in humans.
3. *Evidence that the mechanism results in known disease in humans.* For example, the wild-type infection causes the adverse health outcome, or another vaccine has been demonstrated to cause the same adverse outcome by the same or a similar mechanism.

If the committee identifies evidence of biological mechanisms that could be operational, it will offer a summary judgment of that body of evidence as weak, moderate, or strong. The summary judgment of the strength of the evidence also depends both on the quantity (e.g., number of studies or number of subjects in a study) and quality (e.g., the nature of the experimental system or study design) of the evidence.

Influenza Vaccines and Neurological Complications

The committee's review of the evidence concerning risks that might be associated with influenza vaccines had to take into account a distinctive feature of the vaccine: its formulation changes from year to year to reflect changes in the strains of influenza virus circulating in the population. As a result, the question before the committee actually concerns many different influenza vaccines rather than a single, consistent product used over many years. In terms of the

[1] For a discussion of the evolution of the terminology concerning biological mechanisms, see the committee's earlier reports (IOM, 2001a,b; 2002a,b).

neurological outcomes of concern, GBS is the most widely cited. Other outcomes considered by the committee are multiple sclerosis (MS) and optic neuritis.

Influenza and Influenza Vaccines

Influenza is an acute and highly contagious viral respiratory disease that occurs worldwide. Although some infections are subclinical, influenza is responsible for substantial morbidity and mortality. The elderly, young children, and persons with chronic cardiac or pulmonary diseases are generally at greatest risk for fatal complications (Dolin, 2001). In the United States alone, the disease is now estimated to contribute to an average of 36,000 deaths each year[2], a toll that has risen as the population has aged (Thompson et al., 2003). The extent and severity of influenza infections can vary widely from year to year.

The influenza viruses infects the respiratory epithelium. Onset of illness is often abrupt, with systemic symptoms that include fever, chills, headache, myalgias and respiratory signs such as cough and sore throat. In uncomplicated cases, acute illness typically resolves over 2 to 5 days. Recovery may be complete within a week, but some patients experience persistent weakness or lassitude (Dolin, 2001). Many of the influenza-related deaths result from complications, the most common being secondary bacterial pneumonia. Influenza can also exacerbate chronic pulmonary conditions or contribute to a general deterioration in cardiac or pulmonary function, especially in the elderly or persons with chronic illness.

Influenza viruses are members of the family Orthomyxoviridae. Three forms of the virus—referred to as types A, B, and C—are known to infect humans. The B and C viruses circulate only in humans, with type C producing little illness. Type A viruses, however, circulate not exclusively in humans but also in wild aquatic birds, their natural reservoir. In addition, the type A viruses infect other birds and several species of mammals. Influenza A viruses are subtyped based on antigenic characteristics of their spike-like surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) (Dolin, 2001). Influenza B and C viruses also carry HA and NA surface antigens, but they are not given subtype designations.

Immunity to influenza depends on the formation of antibodies to the glycoprotein surface antigens HA and NA (Dolin, 2001; Hilleman, 2002). However, influenza viruses of types A and B are successful in evading pre-existing immunity from prior infections or vaccination because HA and NA continuously evolve (Dolin, 2001; CDC, 2002a). Replication of the genetic material in the influenza A and B virus genomes is error-prone and there is no proofreading mechanism, allowing for the accumulation of point mutations (Dolin, 2001; Hilleman, 2002; Steinhauer and Skehel, 2002; Ziegler and Cox, 1999). Such mutations in the genes encoding the surface antigens lead to what is called antigenic drift. The influenza A virus is also subject to antigenic shift—a major change in the HA or NA antigens (e.g., from H1 to H2 or N1 to N2). Antigenic drift occurs often, leading the need for annual influenza vaccination. Antigenic shift occurs less frequently and is associated with increases in morbidity and mortality.

Vaccination is the primary means of reducing the impact of influenza. The effectiveness of influenza vaccines depends, in part, on the match between the viral strains used to produce them and the strains that actually circulate in the subsequent influenza season. The Advisory Committee on Immunization Practices (ACIP) currently recommends influenza vaccination for persons 6 months of age and older who are at increased risk for complications of influenza, all persons 50

[2] The authors also report an average of 51,203 all-cause deaths per year from 1990-1999. Deaths in this category include those not directly related to respiratory viral infections, such as, deaths from motor accidents and fires.

to 64 years old, and health care workers and others who can routinely transmit influenza to those at high risk for complications (CDC, 2003c). Persons considered to be at high risk for complications from influenza include persons aged 65 years or older; residents of nursing homes and chronic care facilities; children and adults with chronic lung, heart, kidney, metabolic, or immune system disorders; and women who will be in the second or third trimester of pregnancy during influenza season. The ACIP encourages, when feasible, the use of influenza vaccine for children 6 to 23 months of age.

The vaccines currently approved for use in the United States are inactivated ("killed virus") influenza vaccines.[3] A live attenuated intranasal influenza vaccine was just approved by the FDA in June 2003 for use in the United States in healthy individuals aged 5-49 years (DHHS, 2003).Current vaccines are trivalent, produced using strains of influenza A(H1N1), influenza A(H3N2), and influenza B viruses. Because of the continuing antigenic changes in these viruses, new influenza vaccines are formulated each year based on information on the viral strains that circulated during the previous season or are circulating at the time in other parts of the world.

Adverse Neurological Events

The adverse events considered in this report—GBS, MS, and optic neuritis—are primarily diseases involving demyelination of nerve cell axons in either the central (CNS) or peripheral (PNS) nervous systems.

GBS is an acute, immune-mediated paralytic disorder of the peripheral nervous system. Estimates of the annual incidence of GBS range from 0.4 to 4.0 cases per 100,000 population, with most studies pointing to a level of from 1 to 2 cases per 100,000 (Hughes and Rees, 1997; Magira et al., 2003). GBS occurs throughout the year, and in the United States the condition is more likely to occur in adults than in children (Asbury, 2000).

About two-thirds of GBS cases occur several days or weeks after an infectious event (Hughes and Rees, 1997), commonly a diarrheal illness or a virus-like upper-respiratory infection. From 20 percent to 40 percent of all GBS cases are associated with *Campylobacter jejuni* infections (Buzby et al., 1997). Exposure to certain vaccines has also been associated with an increased risk for GBS. The potential association between GBS and influenza vaccines, most notably the 1976 swine influenza vaccine, has been widely studied and is the subject of this report.

The characteristic clinical feature of GBS is an acute, rapidly progressive, symmetric weakness, with loss of deep tendon reflexes, possible tingling in the feet and hands, and muscle aches (myalgia). Approximately 85 percent of patients will return to normal functioning within 6 to 9 months, but some patients experience relapses or a prolonged disease course with residual neurological deficits (Asbury, 2000; Joseph and Tsao, 2002). The mortality rate is 3-5 percent, with patients succumbing to undetected respiratory failure, malfunction of the autonomic nervous system, or to complications of immobility such as sepsis or pulmonary embolism (Joseph and Tsao, 2002).

MS affects between 250,000 and 350,000 people in the United States and is the most common inflammatory demyelinating disease of the CNS (Keegan and Noseworthy, 2002). Its incidence and manifestations vary within the population. The relapsing-remitting form, for example, occurs predominantly in females (~1.6:1), but follows a more severe clinical course in males (Noseworthy et al., 2000). The incidence of the disease is highest in persons between the ages of

[3] Influenza vaccines licensed for use in the United States for the 2002 influenza season included FluShield, (Wyeth Lederle); Fluvirin, (Evans Vaccines), Ltd.; and Fluzone, (Aventis Pasteur). As of November 2002, Wyeth ceased producing influenza vaccines.

20 and 40 years, but it is also diagnosed in children as young as 2 years and in older individuals. The prevalence of the disease is between 50 and 250 cases per 100,000 population in high-risk areas such as the Scandinavian countries or the northern United States, whereas it is less than 5 cases per 100,000 in Africa and Japan (Waubant and Stuve, 2002).

Clinically, MS is characterized by a variety of neurological signs and symptoms, reflecting the occurrence of inflammatory demyelinating lesions throughout the CNS. Common presenting symptoms include focal sensory deficits, focal weakness, a loss of vision, double vision, imbalance, and fatigue. The severity of the disease can range from subclinical forms that are diagnosed only after death from other causes to hyperacute forms that lead to death within the first few months after disease onset. The cause of MS remains elusive, but disease susceptibility appears to involve both genetic and environmental factors. Genetic factors are reflected in an increased risk of developing MS among family members of MS patients.

Optic neuritis is caused by an inflammation of the optic nerve, with lesions occurring behind the orbit but anterior to the optic chiasm (IOM, 1994a). Symptoms include rapid vision loss, pain associated with eye movement, dimmed vision, abnormal color vision, altered depth perception, and Uhthoff's phenomenon (visual loss associated with an increase in body temperature) (IOM, 2001c). The majority of cases resolve within a few weeks to months of onset. Optic neuritis can occur as an isolated monophasic disease, or it may be a symptom of other demyelinating diseases such as acute disseminated encephalomyelitis (ADEM) or MS.

SCIENTIFIC ASSESSMENT

Causality

Guillain-Barre Syndrome

For its review of the epidemiologic evidence regarding a possible association between influenza vaccination and GBS, the committee separated studies concerning the vaccines administered during the 1976 National Influenza Immunization Program from studies concerning influenza vaccines administered in subsequent years. The committee reviewed studies that presented data for the nation as a whole and studies based on data for individual states or for military personnel. Case reports were also reviewed, but the committee concluded that reports to VAERS and other case reports submitted to the committee are uninformative with respect to causality, although they are useful for hypothesis generation. Case reports help describe the domain of concerns, but the data are usually uncorroborated clinical descriptions that are insufficient to permit meaningful comment or to contribute to a causality argument. The analytical value of data from VAERS and other passive surveillance systems is limited by such problems as underreporting, lack of detail, inconsistent diagnostic criteria, and inadequate denominator data (Ellenberg and Chen, 1997; Singleton et al., 1999).

1976 Swine Influenza Vaccine

Studies that examined the association between swine influenza vaccine and GBS, including analysis and reanalysis of nationwide data (Schonberger et al 1979, Langmuir et al 1984),, and state-based studies (Parkin et al., 1978; Marks and Halpin, 1980; Breman and Hayner, 1984; Safranek et al., 1991) consistently showed an increased risk of GBS for the vaccinated population (See Table 3). **The committee concludes that the evidence favors acceptance of a causal rela-**

tionship between 1976 swine influenza vaccine and Guillain-Barré syndrome in adults. Concerns that the evidence of increased risk found in the original analysis of the national data might have been a reflection of inaccuracies in ascertainment of GBS cases have been addressed in subsequent studies by detailed and systematic reviews of clinical data to verify GBS diagnoses.

Although the studies of GBS among military personnel (Johnson, 1982; Kurland et al., 1986) do not show an association with the 1976 swine influenza vaccine, these studies have limitations that led the committee to discount their findings in its evaluation of the evidence. Military personnel represent a more limited age range than the civilian population and are typically healthier on average than civilians of comparable ages. In addition, information bias may have been present because estimates of the number of vaccinations administered and the number of people serving in the military were not validated and the accuracy of the data sources were not reported. Thus, these studies are limited in their ability to contribute to the causality argument.

Influenza Vaccines Used after 1976

The committee reviewed several population-based surveillance studies (Hurwitz et al., 1981; Kaplan et al., 1982, Lasky et al., 1998), a study of military personnel (Roscelli et al., 1991), and two unpublished studies that were discussed by Chen (2003) at the committee's public meeting (see Table 4). Their findings were mixed. The studies differed in terms of their design, the case definitions for GBS, their methods of case ascertainment, the size of the study populations, and the influenza seasons covered. Compared with the 1976 immunization experience, vaccinations were administered over a longer period of time in the years covered by these studies, making it more difficult to detect any increase that might have occurred in a rare condition like GBS. Although immunization rates were estimated to be much higher among U.S. Army personnel (Roscelli et al., 1991), the relatively small size of the population vaccinated each year would make detection of vaccine-attributable risk difficult. Because of the nature of case reports, the information from VAERS added little to the committee's ability to assess causality.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between GBS in adults and influenza vaccines administered after 1976 (that is, subsequent to the swine influenza vaccine program).

Multiple Sclerosis

The committee examined reports on epidemiological studies of relapses among MS patients following influenza vaccination; separately it examined a smaller set of reports concerning the risk of MS onset. All these studies concerned influenza vaccines used in various years, including the swine influenza vaccines of 1976. The committee was also provided with VAERS summary information (Haber, 2003). Reports from passive surveillance systems like VAERS are of little assistance in assessing causality.

On the basis of the Confavreaux study (2001) and the consistent findings from the other studies (Miller et al., 1997; Mokhtarian, 1997; Bamford, 1978; Myers et al., 1977), **the committee concludes that the evidence favors rejection of a causal relationship between influenza vaccines and relapse of multiple sclerosis in adults.** Uncontrolled studies and case series (De Keyser, 1998; Salvetti et al., 1995; Sibley et al., 1976) provide similar findings, but given their nature they are of limited value in assessing causality. The occurrence of relapse is rare and the power to detect increased risk is limited.

Few studies have examined the association between influenza vaccination and the onset of MS. Only one study (DeStefano et al., 2003) provided a thorough description of the study methods and outcomes. It found no increase in the risk of onset of MS associated with influenza vaccination, but in the absence of confirmation from other sources, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccines and incident MS in adults.** However, the biological mechanisms involved in the onset of MS are presumed to be related to those involved in relapse. With the epidemiological data favoring the rejection of a causal relationship between influenza vaccines and relapse of MS, the committee sees no reason to suspect that a causal relationship might exist between influenza vaccines and onset of MS.

Because the available studies did not consistently report ages (some did not report age at all, and detail is lacking in studies that did report age, for example, reporting average age without a range) and none of the studies specifically included children, the committee could not reach a conclusion on causality in the children's age group, but also could not clearly define the lower age limit for its conclusion in adults.

Optic Neuritis

With a single epidemiologic study available (DeStefano et al., 2003), **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccines and optic neuritis in adults**. VAERS data and case reports have limited value in assessments of causality. Because the available studies that examined optic neuritis did not specifically include children, the committee could not reach a conclusion on causality in the children's age group, but also could not clearly define the lower age limit for its conclusion in adults.

Other Demyelinating Neurological Conditions

Several case reports have been published mentioning the occurrence of other neurological disorders (e.g., acute disseminated encephalomyelitis, transverse myelitis) after influenza vaccination (Saito et al., 1980; Yahr and Lobo-Antunes, 1972; Bakshi and Mazziotta, 1996; Larner and Farmer, 2000). Other neurological conditions were reported from the surveillance system set-up during the 1976 National Influenza Immunization Program, but the data were not sufficient to assess causality (Retailliau et al., 1980). No other epidemiological studies were identified. Based on the nature of case reports and the paucity of epidemiological data, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccines and other demyelinating neurological disorders.**

Children and Influenza Vaccines

Influenza vaccine is generally administered to adults, and relatively few studies have reported data concerning any neurological complications observed in children. Currently, ACIP encourages influenza immunization for children ages 6-23 months (CDC, 2003c). A recommendation for annual routine influenza immunization in that age group may be made within the near future (CDC, 2003c). Given concerns that demyelinating neurological disorders might follow receipt of influenza vaccines, the committee describes the relevant data in children, specifically focusing on the age group 6-23 months .

The published reports concerning the 1976 swine influenza vaccine and GBS (Schonberger et al., 1979; Marks and Halpin, 1980; Breman and Hayner, 1984) and the reports on the safety of trivalent inactivated influenza vaccine in children (Neuzil et al., 2001; Gonzalez et al., 2000; Piedra et al., 1993) did not directly examine the relationship between influenza vaccines and demyelinating neurological disorders in children. These studies use a broad and varied definition of "children," and the small number of children in the studies limit the ability to detect rare neurological outcomes, such as GBS and MS. The committee reviewed one unpublished study that reported no cases of MS or other demyelinating disorders in children (France, 2003), but the unpublished nature of the study and the small number of cases limit its use in assessing causality. No published studies directly examined receipt of influenza vaccines and the occurrence of demyelinating neurological disorders in children. Thus, based on the lack of direct published evidence on influenza vaccines and demyelinating neurological disorders in children, especially those aged 6-23 months, **the committee concludes that there is no evidence bearing on a causal relationship between influenza vaccines and demyelinating neurological disorders in children aged 6-23 months.**

Biological Mechanisms

In its assessment of the possibility of a relationship between influenza vaccines and neurological complications, the committee hypothesized two general ways vaccine could lead to neurological complications: immune-mediated processes and neurotoxic effects.

Infection can induce immune-mediated tissue injury. In most cases, this injury is short-lived and resolves as the immune system eliminates active infection. The injury is a consequence of the immune response to the foreign invader, and when the invader is eliminated, the damaging immune process ceases. In some diseases, however, infection appears to induce an injurious immune response in the form of T and B cells that are directed, at least in part, against self antigens. This autoimmune injury must be distinguished from immune-mediated injury that results from persistent but undetected infection.

The two major mechanisms proposed to account for the activation of self-reactive T and B cells and the induction of autoimmunity by infection are molecular mimicry and bystander activation (see IOM 2002b for a complete review of this issue). *Molecular mimicry* is a mechanism by which an antigenic epitope from an infectious agent or other exogenous substance that is structurally similar to (mimics) an epitope of a self-molecule has the potential to trigger the activation of self-reactive, naïve T or B lymphocytes. *Bystander activation* results when an infection creates environmental conditions that allow the activation of self-reactive T and B cells that are normally held in check. For example, tissue damage from an infection (or an inflammatory process) can lead to the liberation or exposure of host antigens in a context that allows for presentation to, activation of, and expansion of self-reactive lymphocytes.

It is conceivable that vaccine antigens could mimic self (host), that stimulation from vaccines could trigger bystander activation just as an infectious organism does, and that either or both of these potentially damaging mechanisms could possibly lead to the development of central or peripheral demyelinating disease. There is no reason in theory why influenza virus antigens, or other substances in the vaccines (e.g., residual traces of constituents from the production process), could not function in this way. Thus, there is a theoretical basis for influenza vaccines to induce immune responses that could possibly lead to demyelination. As discussed in the subsequent section, however, the evidence in support of this theory is limited, and some is indirect.

The following biological evidence relates to the theory that influenza vaccines could be associated with neurological complications:

- **Bystander activation.** Animal models (Hjorth et al., 1984; Ziegler et al., 1983) show that under contrived experimental conditions inoculation with influenza vaccines in combination with myelin antigens (as tissue or gangliosides) leads to demyelinating diseases similar in many respects to GBS. Animal models of MS-like CNS demyelination also exist but have not been linked to influenza viruses or vaccines. In models of peripheral demyelination (EAN-like disease and EN), influenza vaccines had adjuvant properties in the presence of neural antigens. For this model to operate during routine human use of influenza vaccine, neural injury would have to be initiated during the immunization process to release neural antigens with which the vaccine would act as adjuvant, or influenza vaccines would have to contain myelin (which has not been shown) or other components that mimic myelin.
- **Molecular mimicry.** Evidence related to molecular mimicry is mixed.
  1. No direct evidence shows that influenza antigens or other vaccine components act as molecular mimics of self antigens in the nervous system. Although two older studies demonstrated similarities in amino acid sequences between the myelin protein P2 and the influenza A virus protein NS2, there is no evidence that this sequence similarity leads to structural similarity or that NS2 can elicit host autoantibodies. In addition, NS2 is not likely to be found in influenza vaccines.
  2. A strong set of data indicate that *C. jejuni* antigens can trigger GBS through molecular mimicry. Influenza vaccines are made using viruses cultivated in eggs, and eggs can be contaminated with *C. jejuni*. Although the production of the 1976 swine influenza vaccine by four different manufacturers with four different proprietary seed viruses and different egg sources makes widespread *C. jejuni* contamination seem highly unlikely, the available evidence cannot exclude the possibility that *C. jejuni* antigens were present in the vaccines from all four manufacturers.

The committee concludes that there is weak evidence for biological mechanisms related to immune-mediated processes, including molecular mimicry and bystander activation, by which receipt of any influenza vaccine could possibly influence an individual's risk of developing the neurological complications of GBS, MS, or other demyelinating conditions such as optic neuritis. In the absence of experimental or human evidence regarding the direct neurotoxic effect of influenza vaccines, the committee concludes that this mechanism is only theoretical.

SIGNIFICANCE ASSESSMENT

The committee considered the significance of the concern that influenza vaccines might increase the risk of developing neurological complications such as GBS or MS. The scientific assessment provided support for a link between GBS and the 1976 influenza vaccines, but the evidence for other outcomes or for vaccines for other years was inadequate to support a conclusion or favored no association. Vaccination plays a key role in efforts to reduce the annual impact of influenza infections, making it important that any vaccine-related risks be identified and evaluated.

Influenza vaccine is an essential tool for reducing the substantial burden of morbidity and mortality associated with influenza infections each year. Not only is the yearly disease toll high,

but the prospect of an influenza pandemic is a serious concern to many. If the viral strains used to produce the vaccine are closely matched to the viral strains circulating during the influenza season, vaccination may prevent illness (although not necessarily infection) in 70 to 90 percent of healthy children as young as 6 months of age and healthy adults under age 65. (CDC, 2002b). Vaccination is only 30 to 40 percent effective in preventing illness in older and more frail individuals, but it is 50 to 60 percent effective in preventing hospitalization and 80 percent effective in preventing deaths (CDC, 2002a).

Influenza vaccine must be given every year and is recommended for large segments of the population, making it the one of the most widely used vaccines in the United States. Because the vaccine is used so widely, and may be recommended for regular administration to young children, the possibility of vaccine-related adverse events must be given serious consideration. In its scientific assessment, the committee found support for a causal association between the vaccine used in 1976 and GBS. But it found no support for an association with relapses of MS, and inconclusive evidence regarding influenza vaccines used in other years and other neurological conditions. The committee found no evidence bearing on a causal relationship between influenza vaccines and demyelinating neurological disorders in children aged 6-23 months. GBS is a serious condition, but it is rare and the additional risk related to vaccination in 1976 translated into fewer than 6 cases per million vaccinee (Langmuir et al., 1984). By contrast, influenza contributes to an annual average of 13.8 deaths per 100,000 (36,000 deaths, majority are 65 years of age or older) and to an annual excess of 49 pneumonia and influenza related hospitalizations per 100,000 (114,000 hospitalizations) (Thompson et al., 2003; Simonsen et al., 2000). It is important to fully understand any risk for GBS or other neurological complication that might be associated with influenza vaccination to ensure that it can be appropriately weighed against the sizable burden of illness associated with influenza infections.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

Policy Review

The committee does not recommend a policy review of the recommendations for influenza vaccination by any of the national or federal vaccine advisory bodies on the basis of concerns about neurological complications. Current and future immunization policies should continue to reflect the benefits of influenza vaccination.

Research

With a vaccine as widely used as influenza vaccine, the committee considers it important to pursue research and research-related activities aimed at ensuring that any risk of GBS or other neurological complications is minimized.

Surveillance and Epidemiological Studies

Even though use of the vaccine generally appears to pose minimal risk of adverse neurological events, the strong association between the 1976 vaccine and GBS points to the need for appropriate vigilance through adequate surveillance systems and for better tools to support studies of rare adverse events. **The committee recommends increased surveillance of adverse events associated with influenza vaccination of children, with particular attentiveness to detecting and assessing potential neurological complications. Enhanced surveillance should be in**

place before an ACIP recommendation is made for universal annual influenza vaccination of young children.

Better methods are needed to identify and assess risks for rare outcomes such as the neurological complications considered in this report. The scale of the 1976 vaccination program helped make detection of the link with GBS feasible. **The committee recommends efforts to develop techniques for the detection and evaluation of rare adverse events and encourages the use of administrative databases and the standardization of immunization records as part of this effort.**

Basic and Clinical Science

Despite improvements over the past 25 years in the broad understanding of the pathogenesis of autoimmune diseases, and of GBS in particular, the exact mechanisms by which the 1976 influenza vaccine precipitated this adverse outcome remain unknown. To gain further insight into these mechanisms, the committee sees a need for additional basic and clinical research on influenza viruses, the composition and immunological properties of the 1976 vaccine, immunological responses to vaccines in general, and host characteristics that may affect susceptibility to adverse events.

There is a need to better understand the immunological responses in recipients of the 1976 swine influenza vaccine who experienced GBS. One avenue of inquiry should be the pathogenesis of influenza viruses in general and the swine influenza strain (A/New Jersey/76) in particular to learn whether and how strains might differ in their ability or predisposition to produce neurological injury. **The committee supports ongoing research aimed at better understanding the pathogenesis of influenza and encourages efforts to anticipate which strains might be more neurologically active.**

Although the 1976 influenza vaccine was produced under atypical conditions, with the four manufacturers given less time than usual while being asked to produce much larger quantities than in previous years, there is no evidence that the speed of manufacture or volume of production produced lapses that could have led to a faulty vaccine. The increased risk of GBS associated with the 1976 swine influenza vaccine appeared consistent for vaccine from the four different manufacturers, for the monovalent and bivalent vaccines, and for the whole- and split-virus vaccines. The consistency of the risk across the sources and types of vaccine argues against, but does not rule out, problems related to the manufacturing process. Issues that might be investigated include whether there was something atypical about the nonviral components of the swine influenza vaccines and, if so, identifying it and determining whether it can be controlled.

The use of eggs to produce vaccine-strain influenza virus suggests the possibility that unrecognized antigens might have been present in the 1976 vaccine. *C. jejuni* infection is a recognized risk factor for GBS, possibly acting through molecular mimicry, and *C. jejuni* commonly infects chickens. Although the committee concluded that molecular mimicry is only theoretically possible as an immune mechanism by which influenza vaccines may cause GBS, the evidence that *C. jejuni* antigens can trigger GBS is strong, and the possibility cannot be excluded that *C. jejuni* antigens were present in swine influenza vaccine from all four manufacturers of the 1976 swine influenza vaccine. **Although stocks of the 1976 vaccine are unlikely available, the committee recommends that if samples of the influenza vaccines used in 1976 are available, they should be analyzed for the presence of *C. jejuni* antigens, NS1 or NS2 proteins, or other possible contaminants. The 1976 vaccines should be compared with current and other historical influenza vaccines.**

Studies in animals (Hjorth et al., 1984; Ziegler et al., 1983) have provided at least some basis for considering bystander activation as a potential mechanism by which influenza vaccines could cause GBS or related neurological complications. As it did in a previous report (IOM, 2002a), **the committee recommends continued research using animal and *in vitro* models, as well as with humans, on the mechanisms of immune-mediated neurological diseases that might be associated with exposure to vaccines.**

Genetic factors are known to be an important source of variability in the responses of the human immune system and in the risks of autoimmune disease. At present, understanding of the complex interactions among genetic variables and environmental exposures, including vaccines and wild-type infectious organisms, remains incomplete. **The committee recommends continued research efforts aimed at identifying genetic variability in human immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.**

Communication

A broader framework for influenza vaccine issues is critical for substantial progress in vaccination rates to be achieved. A rigorous, systematic identification of the influences that affect experts' and subpopulations' views and decisions about vaccines is an important step toward developing such a framework (Bostrom, 1997). Despite the studies that have been conducted to date, a comprehensive context has not yet been compiled for the influenza vaccine. **The committee recommends that research be supported to conduct investigations that would deepen and expand the knowledge available from existing studies and more effectively organize what is currently known from these and future projects.** Comprehensive influence diagrams of expert and at-risk populations' views of the vaccine are needed to provide a broader context and reveal richer insights than are possible from a review of currently available studies.

Box ES-1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence favors acceptance of a causal relationship between 1976 swine influenza vaccine and Guillain-Barré syndrome in adults.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between GBS in adults and influenza vaccines administered after 1976 (that is, subsequent to the swine influenza vaccine program).

The committee concludes that the evidence favors rejection of a causal relationship between influenza vaccines and relapse of multiple sclerosis in adults.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccines and incident MS in adults.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccines and optic neuritis in adults.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccines and other demyelinating neurological disorders.

The committee concludes that there is no evidence bearing on a causal relationship between influenza vaccines and demyelinating neurological disorders in children aged 6-23 months.

Biological Mechanisms Conclusions

The committee concludes that there is weak evidence for biological mechanisms related to immune-mediated processes, including molecular mimicry and bystander activation, by which receipt of any influenza vaccine could possibly influence an individual's risk of developing the neurological complications of GBS, MS, or other demyelinating conditions such as optic neuritis.

In the absence of experimental or human evidence regarding the direct neurotoxic effect of influenza vaccines, the committee concludes that this mechanism is only theoretical.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of the recommendations for influenza vaccination by any of the national or federal vaccine advisory bodies on the basis of concerns about neurological complications. Current and future immunization policies should continue to reflect the benefits of influenza vaccination.

Research

The committee recommends increased surveillance of adverse events associated with influenza vaccination of children, with particular attentiveness to detecting and assessing potential neurological complications. Enhanced surveillance should be in place before an ACIP recommendation is made for universal annual influenza vaccination of young children.

The committee recommends efforts to develop techniques for the detection and evaluation of rare adverse events and encourages the use of administrative databases and the standardization of immunization records as part of this effort.

Basic Science and Clinical Research

The committee supports ongoing research aimed at better understanding the pathogenesis of influenza and encourages efforts to anticipate which strains might be more neurologically active.

Although stocks of the 1976 vaccine are unlikely available, the committee recommends that if samples of the influenza vaccines used in 1976 are available, they should be analyzed for the presence of *C. jejuni* antigens, NS1 or NS2 proteins, or other possible contaminants. The 1976 vaccines should be compared with current and other historical influenza vaccines.

The committee recommends continued research using animal and *in vitro* models, as well as with humans, on the mechanisms of immune-mediated neurological diseases that might be associated with exposure to vaccines.

The committee recommends continued research efforts aimed at identifying genetic variability in

human immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.

Communication

The committee recommends that research be supported to conduct investigations that would deepen and expand the knowledge available from existing studies and more effectively organize what is currently known from these and future projects.

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