

SYMPOSIUM

Monitoring Vaccine Safety During an Influenza Pandemic

John Iskander*, Penina Haber, and Guillermo Herrera

Immunization Safety Office, Office of the Chief Science Officer, Office of the Director, Centers for Disease Control and Prevention, Atlanta, Georgia

In the event that a vaccine is available during an influenza pandemic, vaccine safety monitoring will occur as part of comprehensive public health surveillance of the vaccination campaign. Though inactivated influenza vaccines have been widely used in the United States and much is known about their safety profile, attention will need to be paid to both common self-limited adverse reactions and rarer, more serious events that may or may not be causally related to vaccination. The primary surveillance systems used to generate and test hypotheses about vaccine safety concerns are the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), respectively. Examples of recent use of these systems to investigate influenza vaccine safety and enhancements planned for use during a pandemic are presented. Ethical issues that will need to be addressed as part of an overall vaccine safety response include risk communication and injury compensation. Advance planning and the use of available technologic solutions are needed to respond to the scientific and logistic challenges involved in safely implementing mass vaccination during a pandemic.

INTRODUCTION

In the event that a vaccine is available in time to respond to an influenza pandemic [1], the safety profile of such a vaccine will likely be less certain than that of previously released influenza vaccines. As such, the safety of this vaccine will need to be closely monitored. In order to appreciate the scientific and ethical issues involved in ensuring vaccine safety, it is important to understand the historical con-

text and current scientific framework of United States immunization safety activities. This paper will then briefly summarize the current state of knowledge regarding the safety of inactivated influenza vaccines (IIV)[†]. It will conclude with limited discussion of some ethical aspects of safety monitoring, as well as key scientific and programmatic challenges that must be faced to assure the safety of a pandemic influenza vaccine.

*To whom all correspondence should be addressed: John Iskander, Centers for Disease Control and Prevention, 1600 Clifton Rd MS E-61, Atlanta, GA 30333. Tel.: 404-639-8889; Fax: 404-639-8834; E-mail: jxi0@cdc.gov.

[†]Abbreviations: FDA, Food and Drug Administration; GBS, Guillain-Barré Syndrome; IIV, inactivated influenza vaccines; OPV, oral poliovirus vaccine; VAERS, Vaccine Adverse Event Reporting System; VAPP, vaccine-associated paralytic polio; VSD, Vaccine Safety Datalink.

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BACKGROUND

Vaccine-preventable disease surveillance encompasses surveillance for disease burden, vaccination coverage, and vaccine adverse events [2]. Given the likelihood that limited amounts of vaccine may initially be available in the early phases of a pandemic, and having seen the recent experience with the 2004-05 influenza vaccine shortage, prioritizing and tracking of vaccine supply also will be important. Vaccine safety monitoring will need to be an integral part of comprehensive surveillance of the pandemic influenza vaccination program [3].

Mass vaccination campaigns, like those that will occur during an influenza pandemic, may be accompanied by vaccine safety concerns. The "Cutter Incident," which resulted in cases of poliomyelitis due to inadequately inactivated polio vaccine in the 1950s, is an important historical example of safety concerns that arose in the course of a mass vaccination campaign [4,5]. A more recent example involved the 1976-77 swine influenza ("swine flu") vaccine and its association with Guillain-Barré Syndrome (GBS) [6]. Whether such concerns are scientifically validated or not, they have the potential to adversely affect public acceptance of vaccination, especially when there is extensive media coverage [7]. The ability to study and address these concerns is one of the primary reasons for having robust systems for assessing vaccine safety.

Unlike vaccine efficacy and effectiveness, vaccine safety cannot be directly measured. Instead, it is inferred from the relative absence of adverse events. An adverse event following immunization is "...a medical incident that takes place after an immunization, causes concern and is believed to be caused by the immunization" [8]. This definition does not imply any proven causal connection to vaccination. The term "adverse reactions" refers to untoward effects of vaccination unrelated to the vaccine's primary purpose [9].

Formal epidemiologic study is usually required to distinguish between coincidental adverse events and causally related adverse reactions [10]. In rare instances, proof of causality may also be obtained by the finding of a unique clinical syndrome or laboratory result that would not occur in the absence of vaccination. The rare occurrence of vaccine-associated paralytic polio (VAPP) with isolation of vaccine virus strain derived from oral poliovirus vaccine (OPV) is a notable example [11].

CHARACTERISTICS OF INFLUENZA VACCINES

Because influenza vaccines often have different antigenic compositions from year to year, the safety of annual influenza vaccines may vary slightly. Unlike annual influenza vaccines, whose composition includes two circulating A strains and one B strain [12], the pandemic influenza vaccine is projected to be a monovalent vaccine. Most influenza vaccines are given as a single dose per season [12]. In contrast, it is widely anticipated that vaccination with the pandemic strain-based vaccine will require two doses given four weeks apart [13]. The need for a two-dose strategy will need to be taken into account in planning for safety monitoring.

The current egg-based influenza vaccine production technology is constrained by the availability of eggs and is labor-intensive and time-consuming. New methods of producing vaccines are being developed. The main effort is to develop cell-culture methods, providing the capacity of a rapid vaccine production scale-up [14, 15]. Cell-based technology has potential safety issues; these include the possibly unknown biological properties of viruses that may be latent in cell lines, and of solvents, emulsifiers, and preservatives used during cell line and vaccine production. The remote possibility of low-level vaccine contamination by bovine or porcine viruses, or prions derived from cell culture

media must also be considered [16]. New vaccines using cell-derived technologies may require long-term follow-up to ensure their safety [17].

Vaccines are manufactured in batches referred to as lots. Although production follows rigorous quality control processes, bacterial contamination is possible, as occurred at the Chiron plant in Liverpool in 2004 [18]. Although all lots have to pass stringent safety standards [19], inherent biological variability from lot to lot might manifest itself as a difference in the safety profile [20].

TYPES OF ADVERSE EVENTS STUDIED

Local and mild systemic reactions, including pain and swelling at the injection site and fever, are relatively common following inactivated vaccines such as IIV but are almost always self-limited [2]. Such adverse reactions are readily attributable to vaccination [10, 21], and their rate of occurrence can often be estimated from pre-licensure studies [12]. While minor unexpected reactions have occurred with past influenza vaccines [22], it is likely that during an influenza pandemic less attention will be paid to self-limited adverse events.

Because of limits in the size of vaccine trials, rare, potentially serious adverse reactions may not be detected before licensure and/or more widespread use of a specific vaccine [20, 23]. These include immediate allergic reactions (anaphylaxis), which may be related to either an active vaccine component or an additive [2]. Thankfully, true anaphylactic reactions appear to be very infrequent across vaccine types [24]. Despite extensive worldwide experience with use of influenza vaccines, the possibility of heretofore undescribed adverse reactions occurring following widespread use of a pandemic strain influenza vaccine must be considered.

Though GBS has not been consistently associated with influenza vaccines used

after 1976-77, there will be a need to monitor occurrence of GBS following use of pandemic influenza vaccine. Surveillance systems have been in place to detect post-vaccination GBS for at least the past 15 years [25]. Because of the rarity of this event, epidemiologic study of causal attribution may be difficult [26].

Particularly in mass vaccination campaigns, there may be concern about vaccine administration errors. Observing standard immunization practices may reduce the occurrence of such incidents [9, 27]. Because of the potential for serious errors, such as substitution of a therapeutic injectable product for a vaccine [28], surveillance for preventable vaccine misadministration may be warranted.

Systematic study will often find that adverse events may be related to vaccination only temporally without evidence of a causal relationship. The initial signal of concern related to the swine flu vaccine did not involve GBS, but rather a cluster of myocardial infarctions that was subsequently found to be a temporal coincidence [6]. A more recent example involving influenza vaccine involves asthma exacerbations, which were found to be related not to vaccination, but to underlying disease severity [29].

VACCINE SAFETY DATA REQUIREMENTS AND CURRENT PUBLIC HEALTH INFRASTRUCTURE

The fundamental data needed to study vaccine safety is knowledge of the rate of the adverse event being studied in the vaccinated compared to the unvaccinated individuals [30]. The known or hypothesized risk window following vaccination, which is analogous to the incubation period for an infectious disease, must also be taken into account. The risk window might correspond to the peak period of viral replication following use of a live attenuated viral vaccine such as measles/mumps/rubella

[31]. Ascertainment of these types of data was typically done in the past using resource intensive ad hoc studies [32-34].

The public health systems used to monitor the safety of vaccines trace their origins to the National Childhood Vaccine Injury Act of 1986 [35]. The Vaccine Adverse Event Reporting System (VAERS) serves as an "early warning" system for potential vaccine safety concerns [36]. It is jointly operated by the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA). VAERS is a passive surveillance system in which reporting occurs at the national level, rather than locally as with communicable diseases. Reports may be submitted by health care providers, patients, state and local health departments, or by any person who wishes to report an adverse event following vaccination.

VAERS has well-described strengths and limitations. The system collects reports nationally and has been able to rapidly detect rare events in a cost-effective manner. It is also simple: Health care providers or patients only have to fill out a one-page form and mail or fax the report to a centralized office. Secure electronic reporting via the Internet is also available [37]. VAERS allows the rapid generation of hypotheses that can be further tested in controlled studies. VAERS has successfully alerted public health authorities about safety concerns involving rotavirus, yellow fever, and smallpox vaccines, among others [38-40]. Additionally, when concerns have arisen about the need to monitor a specific lot of vaccine, VAERS data have proven useful [41].

It is important to recognize that VAERS is subject to under-reporting, reporting biases (which may be related to media coverage) and reporting of events that are unconfirmed or incompletely described [42]. The degree of underreporting of a specific type of event is not routinely known, though serious events are more likely to be reported [43, 44]. Case definitions developed by the Brighton

Collaboration, an international voluntary organization, provide some assurance that adverse events are counted and categorized in a standardized manner [45]. In its current configuration, the VAERS system does not permit calculation of incidence rates of adverse events in a population.

A variety of data systems is used to assess the distribution of influenza vaccines or estimate the number of persons who have been vaccinated. This denominator information helps to provide context to numbers of reports received by VAERS. These include Biologics Surveillance data derived from vaccine manufacturers [41], population-based immunization coverage surveys such as the National Immunization Survey [46], and U.S. Census population estimates. There is no nationwide registry of the number of people who annually receive influenza vaccine.

Concerns that emerge from VAERS may be either confirmed [47] or refuted [48] by subsequent study. The primary mechanism used for vaccine safety hypothesis testing is the Vaccine Safety Datalink (VSD). The VSD project is a collaboration between CDC and several geographically diverse health maintenance organizations (HMOs); it collects information on enrollees' vaccination status, health outcomes, and demographic characteristics. The VSD covers about 3 percent of the U.S. population [49]. VSD allows assessment of the rate with which medical events occur in both vaccinated and unvaccinated persons. Verification of diagnoses coded in automated data can be accomplished through chart review, and the VSD has been used for studies needed to answer urgent public health questions, most notably when it confirmed the association of intussusception with the first U.S. licensed rotavirus vaccine [47].

However, even a large database such as the VSD may not be sufficiently powerful for detection of extremely rare events such as GBS [R. Davis, personal communication]. Other limitations include limited

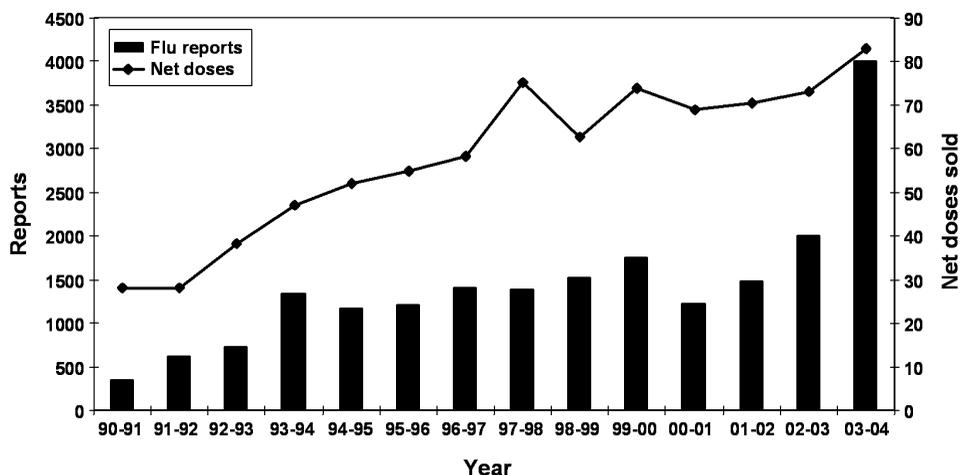


Figure 1. Influenza reports to VAERS by vaccination date, 1/1/1990 to 12/31/04.

access to medical encounters that patients have outside of the HMO setting and potential lack of demographic diversity of the covered population. Because HMOs tend to be early adopters of vaccines due to their emphasis on preventive interventions, specific studies may have relatively small unvaccinated populations.

CURRENT STATUS OF KNOWLEDGE ABOUT THE SAFETY OF INFLUENZA VACCINES

From January 1, 1990, through December 31, 2004, VAERS received 20,193 reports involving influenza vaccine. Figure 1 indicates the increase in influenza vaccine associated reports to VAERS, which has occurred in parallel with increased vaccine distribution. For the 2003-04 influenza season, nearly 3,000 influenza vaccine adverse event reports were received. This spontaneously reported safety data spans across age groups (Figure 2); the number of reports among children has recently increased following expanded vaccine recommendations. Both VSD and VAERS have recently published safety reviews of IIV in children [46, 50], with both reviews indicating a favorable

safety profile. The most commonly reported adverse events in both children and adults are local and mild systemic reactions, similar to those described in clinical trials of influenza vaccines (Table 1).

GUILLAIN-BARRÉ SYNDROME AND INFLUENZA VACCINES

GBS is an acute, immune-mediated, paralytic disorder of the peripheral nervous system. The estimated annual incidence ranges from 0.4 to 4.0 per 100,000 persons [51]. From 20 to 40 percent of all GBS cases are associated with *Campylobacter jejuni* infections [52]. Concerns about the risk of developing GBS after influenza vaccination have been present since the association was first noticed during 1976-77 “swine flu” vaccination campaign. Among persons who received the A/New Jersey swine influenza vaccine, the rate of GBS exceeded the background rate by slightly less than 10 cases per million persons vaccinated; this corresponded to relative risks that ranged from 4.0 to 7.6 for the six- or eight-week period after vaccination [32].

A two-fold increase in the number of cases of GBS after the receipt of influenza vaccine was reported to VAERS during the

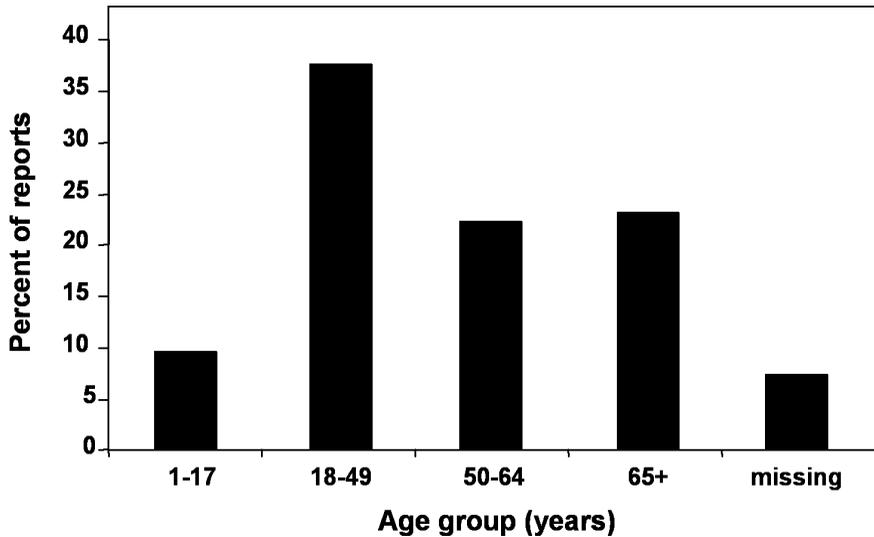


Figure 2. VAERS influenza vaccine reports by age, 1990 to 2004.

1993-94 influenza season. The CDC and the University of Maryland School of Medicine undertook a collaborative investigation to estimate the relative risks associated with vaccination against influenza during the 1992-93 and 1993-94 seasons. The overall risk for the two seasons was 1.7 (95 percent CI: 1.0 to 2.8; $p = .04$) during the six weeks following vaccination, indicating an attributable risk of slightly more than one additional case of GBS per million persons vaccinated [26]. More recently, VAERS researchers have demonstrated a

consistent decrease in GBS reports over time, during a period when overall flu vaccine adverse event reporting and dose distribution was increasing [25]. This decrease in influenza vaccine-associated GBS reports was consistent across all age groups (Figure 3). However, symptom onset interval and preceding illness characteristics following influenza vaccination suggested the possibility of a causal relationship.

In 2003, the Institute of Medicine concluded that evidence was inadequate to accept or reject a causal relationship

Table 1. Most frequently reported influenza vaccine adverse events*: VAERS 1990 to 2004.

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|--|
| Children (<18 years old): |
| <ul style="list-style-type: none"> • Reactions at the injection site • Fever • Pain and swelling at the injection site • Vasodilatation (flushing) |
| Adults (≥18 years old): |
| <ul style="list-style-type: none"> • Reactions at the injection site • Vasodilatation • Fever • Pain • Myalgia (muscle aches) |

*Reports may involve more than one adverse event

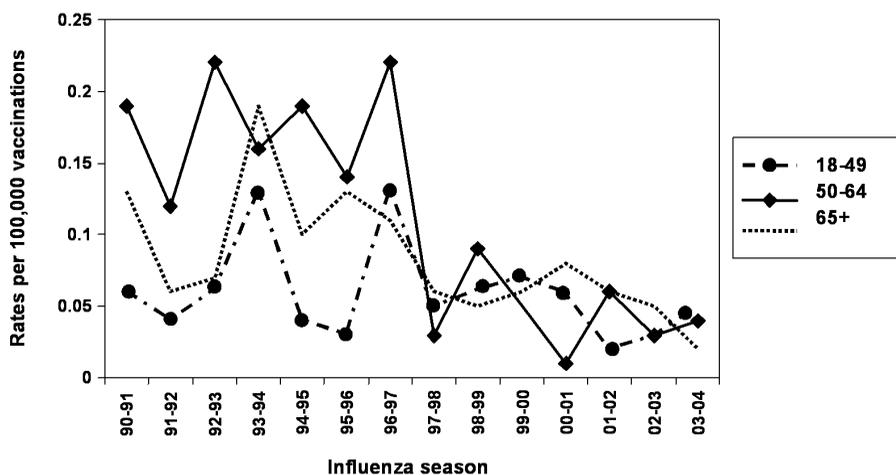


Figure 3. GBS reporting rates by age and influenza season, VAERS 1990-2004.

between GBS in adults and influenza vaccines administered after 1976, but recommended utilizing new laboratory techniques to re-examine the swine flu vaccine in order to better understand the pathophysiologic basis of swine flu vaccine-induced GBS [53]. The CDC is currently funding a study that is looking at a variety of hypotheses related to whether the vaccine virus, another vaccine component, or potential bacterial contamination with *Campylobacter jejuni* was responsible for causing swine flu vaccine-associated GBS.

OTHER SERIOUS ADVERSE EVENTS OF POTENTIAL SIGNIFICANCE

Bell's palsy (BP) is a paralysis of the nerves of the face from which people tend to recover fully. In 2000-01, BP was associated with a Swiss-licensed inactivated virosomal subunit intranasal influenza vaccine, a product that was never licensed or used in this country [54]. It contained *Escherichia coli* heat-labile toxin as a mucosal adjuvant, which may have been responsible for the development of BP [55]. When a follow-up study in VAERS indicated the possibility of an association between IIV and BP [56], a population-based VSD study was launched

to assess the validity of this hypothesized link. This example illustrates the potential for conducting coordinated studies within VAERS and the VSD.

Allergic reactions are typically accepted to be causally related to vaccination. The evidence indicates that episodes of anaphylaxis (and allergic reactions in general) are quite rare following all vaccines [24], though studies specifically quantifying the influenza vaccine associated risk have not been done in adults. Rare but serious anaphylactic reactions may very well be related to the vaccine's egg protein content, and persons with known allergy to eggs should not be vaccinated [12].

ETHICAL ASPECTS OF PANDEMIC INFLUENZA VACCINE SAFETY

Basic assumptions about pandemic influenza vaccine include high demand, limited supply, need for vaccine priorities, possible use of new technologies, and distribution prior to thorough evaluation of the product's safety profile. A vaccine safety surveillance system will have to anticipate possible problems while conducting effective surveillance of the product during its use. The need to detect adverse events in a timely manner will

need to be balanced against issues of disease severity and vaccine efficacy.

For any licensed vaccine, a Vaccine Information Statement (VIS) is the legally mandated document that must be provided to individuals prior to vaccination. Informed consent is not formally required. The VIS for a pandemic influenza vaccine would likely be similar to that for currently licensed influenza vaccines, in which there is discussion of both common and rare side effects of vaccination [57].

Patients who have experienced prior GBS are currently considered to have a precaution to further vaccination, meaning that the risks and benefits must be weighed for each individual patient. Though GBS is a serious condition, requiring hospitalization and often intensive care, it is rare. In contrast to the swine flu vaccination campaign which caused fewer than one GBS case per 100,000 vaccinees, influenza contributes to an annual average of 36,000 deaths and more than 200,000 hospitalizations [58, 59].

A pandemic influenza vaccination program will likely include some provisions for persons claiming vaccine-related injuries. The Vaccine Injury Compensation Program (VICP) is a "no fault" federal program designed to compensate individuals thought to have been harmed by vaccines [60]. As of July 1, 2005, trivalent influenza vaccines (inactivated) are now covered under VICP. The 1976-77 swine influenza vaccine campaign also was linked to a federally funded compensation program.

CONCLUSION: PANDEMIC VACCINE SAFETY CHALLENGES AND OPPORTUNITIES

Expansion of influenza vaccination in the setting of an influenza pandemic will pose challenges in monitoring vaccine safety. The VAERS and VSD systems will be on the frontline of early safety "signal detection" should widespread use of a pandemic influenza vaccine occur. Since 2002, VAERS has accepted secure web-

based electronic reporting; this has resulted in more timely and complete adverse event reporting [61]. VAERS will be further enhanced through activation of an emergency preparedness plan, which will allow processing of much larger numbers of reports than are currently received, along with near real-time notification of significant adverse events. Active surveillance for adverse events, a capability recently developed by the VSD [62], will provide data more rapidly. In the setting of a pandemic, analyses for specific safety outcomes of interest, such as GBS, will be conducted weekly. The VSD can also provide age-specific background rate data for medical events of interest [63]. Availability of age-specific dose administration data, which could be captured and linked to adverse event reports by bar-coding [64], linkage to immunization registries [65], or within the VSD, would allow calculation of adverse event rates for persons receiving first and second doses.

Creation of additional safety infrastructure or enhancement of existing systems, including clinical vaccine safety provider networks [66], may be needed to meet the safety needs of expanded influenza vaccination. Though serious events such as allergic reactions and GBS are rare, focused study will be required to determine if they are causally related to vaccination. Rare risks of potentially serious events present both scientific and communication challenges [67].

Existing safety systems have successfully monitored a broad spectrum of influenza vaccine-related issues. A pandemic vaccination campaign may well yield more vaccine safety data of greater complexity than is seen with annual influenza vaccination. Key factors in continued robust surveillance will include optimal use of new technologies, linkages with other immunization surveillance systems, and a commitment on the part of public health to support vaccine safety surveillance proactively through advance preparation [68].

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