11 Public health surveillance for vaccine adverse events

John K. Iskander[1] *& Yenlik Zheteyeva*[2]

[1]Office of the Associate Director for Science, Centers for Disease Control and Prevention, Atlanta, GA, USA

[2]National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Introduction

Monitoring of the safety of vaccines and immunizations is an integral and vital part of vaccine-preventable disease (VPD) surveillance. Given the importance of immunization and its widespread use as a preventive intervention, public health officials and scientists should possess a working knowledge of the systems and methods used to evaluate vaccine safety, which differ from those used in VPD surveillance (see Chapter 10). Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem. Vaccine vigilance or vaccinovigilance is a specialized branch of pharmacovigilance that involves the surveillance of the safety of vaccines and immunizations.

This chapter will describe the rationale for undertaking systematic vaccine safety surveillance, as well as the historical context in which such activities have become increasingly important with the maturing of immunization programs worldwide [1]. Regulatory and programmatic aspects of vaccine safety systems will be outlined briefly. Key methodologic concepts and definitions, including the distinctions between active and passive surveillance systems, will be summarized. Finally, two case studies integrating key scientific and public health concepts will be presented.

Objectives of vaccine safety surveillance

Before a vaccine is approved for use, prelicensure trials must be conducted to establish its efficacy and safety. However, these trials are seldom large enough to be able to detect reactions with incidences of less than 1 in 10 000. Postlicensure monitoring of vaccine safety is therefore necessary for detection of rare or novel adverse reactions not identified in prelicensure trials [2]. Because vaccines are primarily given to healthy persons for prevention of disease, the tolerance for serious reactions is much lower than for drugs that are administered to ill persons for therapeutic or curative purposes. Very rare serious vaccine reactions with attributable risks as low as one per 100 000 doses [e.g., Guillain–Barré syndrome (GBS) after the 1976–7 swine influenza vaccine] [3] or even one per million doses (e.g., paralysis after oral poliomyelitis vaccine) [4] have resulted in withdrawal of vaccines or changes in immunization policy. Even uncommon vaccine adverse reactions may result in considerable numbers of affected individuals (e.g., more than 100 reported cases of intussusception occurred following licensure of the first rotavirus vaccine, despite an attributable risk of only one per 10 000 doses [5]).

Postlicensure monitoring is also necessary to assess the safety of new vaccines among populations commonly excluded from clinical trials, including the elderly, those with chronic medical conditions, and

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pregnant women. Safety monitoring may uncover elevated risk for adverse events among these groups once vaccine licensure permits broader use of a new vaccine [6]. Postlicensure study also can help to resolve vaccine safety controversies and reassure the public. For example, concerns about a causal association between tetanus toxoid and spontaneous abortions among vaccinated pregnant women in the Philippines hampered efforts to control neonatal tetanus. Immunization rates increased once an epidemiologic study refuted the association [7].

Programmatically, surveillance of an immunization program can be conceived of as a "three-legged stool," with coordinated monitoring of VPD levels, vaccine coverage, and risks from vaccines. Monitoring vaccine safety plays an important role in maintaining public confidence needed to keep vaccination levels above disease prevention thresholds [8]. Concerns about the combined measles, mumps, and rubella (MMR) vaccine's alleged link to autism led to decreased vaccine uptake in the UK and an upsurge in reported measles cases [9]. Following scientific refutation of these charges, MMR coverage rates have increased.

Historical and public health context of vaccine safety

Concerns about the safety of vaccines date back to Jenner's initial use of cowpox as a vaccine against smallpox [10]. The 1955 "Cutter incident," in which several inadequately inactivated lots of the newly developed Salk polio vaccine caused disabling or fatal polio in 174 persons [11], was one of the first modern field investigations of vaccine safety (Figure 11.1). With the near elimination of the target VPDs owing to high vaccine coverage in many countries with well-developed immunization programs, vaccine safety issues paradoxically became more prominent (Figure 11.2). This new paradigm is illustrated by the more recent history of smallpox vaccine. When studies undertaken during the late 1960s documented the burden of adverse reactions to smallpox (vaccinia) vaccine, the result was a policy decision to discontinue its routine use in some countries prior to smallpox eradication [12,13]. The rare association of GBS with the 1976–7 "swine flu" vaccine mass campaign in the USA led to the development of the US vaccine safety infrastructure [3,14]. Concerns about the safety of the whole-cell pertussis vaccine globally led to the rise of vaccine consumer groups, lawsuits, loss of vaccine manufacturers, vaccine injury compensation programs, and finally a less reactogenic acellular vaccine [8]. The late 1980s and early 1990s saw the initiation of many current vaccine safety surveillance systems in the USA [15,16]. During the late 1990s high-profile vaccine safety concerns were based on proven adverse events as well as rumors and inconclusive studies. There was a proven association between the first licensed rotavirus vaccine and intussusception [17,18], hypothesized (but scientifically unsupported) issues including alleged links between MMR and autism [19], concern about the mercury-containing preservative thimerosal [20], and rumors about contamination of oral polio vaccine (OPV) used as part of polio eradication campaigns [21].

Unlike communicable disease surveillance, which operates primarily at subnational levels, some aspects of vaccine safety monitoring are governed by national regulatory requirements. General roles of national regulatory authorities (NRAs), such as the US Food and Drug Administration (FDA) and the European Medicines Agency, include requiring postlicensure studies as a condition of new vaccine licensure [22], mandating that manufacturers submit spontaneously received adverse event reports [23], and initiating label changes or other regulatory actions, including product withdrawal, based on review of safety surveillance data. NRAs are also involved in monitoring the purity, efficacy, and safety of individual vaccine lots, both prior to their release and during their general use [2].

Definition and categorization of adverse reactions to vaccines

Rather than being directly measured, vaccine safety is inferred from the absence of new adverse events when a functional monitoring system is in place. An adverse event following immunization (AEFI) or vaccine adverse event (VAE) is "... a medical incident that takes place after an immunization ... and is believed to be caused by the immunization" [24]. The term "adverse reaction" or side effect refers to untoward effects of vaccination caused by the vaccination [25]. AEFIs may include: (1) true adverse reactions; (2) coincidental events that would have occurred even if the person had not been vaccinated; (3) program

Figure 11.1 The children in this class were among the first to receive the newly developed Salk polio vaccine in 1955. The investigation of the "Cutter incident," in which several inadequately inactivated lots of this new vaccine caused disabling or fatal polio, highlighted the importance of vaccine safety [11]. Used with permission from March of Dimes.

errors related to mistakes in vaccine preparation, handling, or administration (e.g., injection site abscesses due to vaccine contamination); and (4) adverse events that cannot be directly related to the vaccine or its administration, or another identifiable cause [26]. Certain reported adverse events are considered "serious" according to regulatory definitions and international criteria [23]. These include events that, according to the reporter, resulted in hospitalization, life-threatening illness, disability, or death.

Vaccine adverse reactions may be grouped into three general categories: local, systemic, and allergic [25]. Local reactions such as pain, swelling, or redness at the site of injection are usually the least severe and most frequent; they are brief, self-limited, and rarely result in complications. Systemic reactions, which may be similar to a mild form of the natural disease (e.g., fever) occur less frequently than local reactions, but only infrequently pose serious risks. These reactions occur more commonly after receipt of live attenuated vaccines such as MMR. Data from some prelicensure trials suggest that some minor systemic events may not be vaccine attributable [27]. Rarely, systemic reactions may be medically serious. Thrombocytopenia

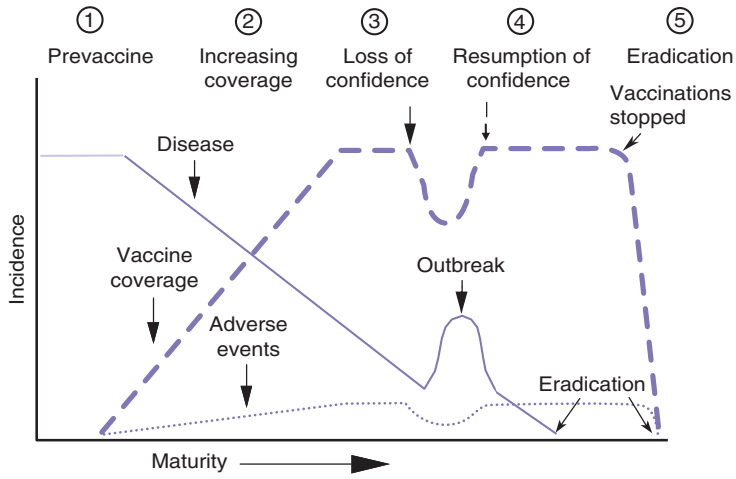

Figure 11.2 Evolution of an immunization program and prominence of vaccine safety. *Source:* Chen *et al.* [15].

occurs following MMR with an approximate incidence of one in 30 000–40 000 vaccinations; however, this is less than its occurrence following either wild measles or rubella infection [28, 29]. Allergic reactions, although the most severe, are the least frequent; the most serious type, anaphylaxis, occurs approximately once per million vaccinations [30].

AEFIs may be classified according to the clinical characteristics of the event and/or the known or suspected relationship to vaccination [25, 26]. Table 11.1 presents examples of adverse events categorized according to both clinical manifestations and relationship to vaccination.

Overview of methods used in adverse event reporting systems

Many national immunization programs have passive surveillance or spontaneous reporting systems (SRSs) for AEFIs. Reviews of case reports can be useful for identifying adverse events of concern that should be evaluated in follow-up studies or inquiries. The US Vaccine Adverse Event Reporting System (VAERS) and the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) are examples of such reporting systems. Vaccine manufacturers also maintain internal safety reporting systems for their

Table 11.1 Classification of adverse events following immunization by clinical characteristics and relationship to vaccination, with illustrative examples

	Local	Systemic	Allergic
Program error	Nerve damage during injection of vaccine	Administration of non-vaccine product with systemic effects	Administration of a vaccine containing an allergenic component to persons with known hypersensitivity to vaccine component (e.g. yeast in hepatitis B vaccine)
Adverse reaction	Cellulitis in injected limb	Fever	Anaphylaxis
Coincidental adverse event	Unrelated conditions at or near injection site (e.g., bites, underlying dermatologic conditions)	Upper respiratory infection following inactivated influenza vaccine	Allergic reaction related to non-vaccine exposure (e.g., infant formula)

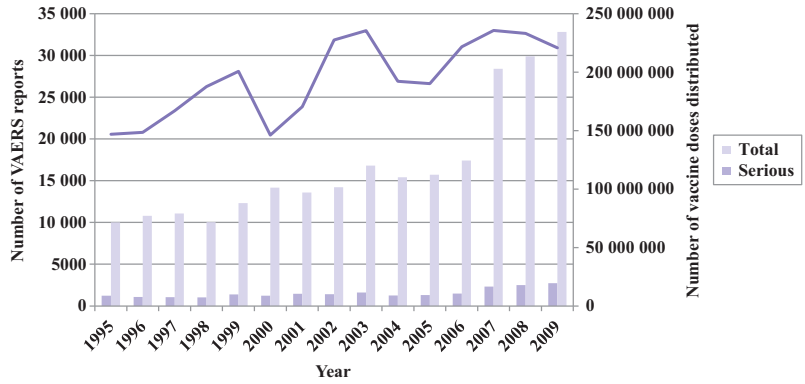

Figure 11.3 Reports to the US Vaccine Adverse Event Reporting System, 1995–2009. *Source:* www.vaers.hhs.gov, US Biologics Surveillance, CDC.

products, and routinely forward all reports to appropriate regulatory authorities.

VAERS is a prototypical surveillance system that serves as an "early warning" system for potential vaccine safety concerns. It is jointly operated by the US Centers for Disease Control and Prevention (CDC) and the FDA and has been operational since 1990 [15]. In contrast to many other countries, where reporting is limited to healthcare professionals [31], VAERS reports may be submitted by healthcare providers, patients, state and local health departments, or by any other person who wishes to report an AEFI. Manufacturers are required to report all adverse events of which they become aware [23].

VAERS, like other SRSs, has strengths and limitations. The system collects reports on a national scale and can rapidly detect rare events in a cost-effective manner. Isolated rare events may become apparent more readily when centrally reported. VAERS allows for the rapid generation of hypotheses that can be further tested in controlled studies. For example, VAERS has successfully alerted public health authorities about safety concerns involving tetravalent rotavirus (intussusception), yellow fever (viscero- and neurotropic disease), and smallpox (myo/pericarditis) vaccines [32–34]. VAERS also has the capacity to monitor specific lots of a vaccine when concerns arise [35]. Figure 11.3 summarizes temporal trends in reporting to VAERS since 1995. Overall reporting has increased, most notably since the introduction of new high-profile vaccines [e.g., human papillomavirus (HPV) in 2007] and institution of mass campaigns (e.g., pandemic H1N1 influenza in 2009–10). However, the number of reports meeting FDA criteria for seriousness has remained relatively low.

Except for injection site reactions, some immediate-type allergic reactions, recurrence of unique symptoms following subsequent vaccinations [36], or occurrence of a unique clinical syndrome or laboratory result that would not occur in the absence of vaccination (e.g., the rare occurrence of vaccine-associated paralytic poliomyelitis with isolation of vaccine virus strain derived from OPV [37]), it is usually not possible to definitively state that a vaccine caused the reported event [38]. Because case reports usually do not contain all of the information needed for epidemiologic assessments (Figure 11.4), elevated risks of specific adverse events following immunization are best demonstrated epidemiologically through a controlled study. VAERS is also subject to other limitations including underreporting, reporting biases (which may be related

		Adverse event: Yes	Adverse event: No
Vaccination	Yes	a	b
	No	c	d

Figure 11.4 Establishing causality for vaccine adverse events. Rate in vaccinated persons = a/a + b. Rate in unvaccinated persons = c/c + d. Spontaneous reporting systems only receive data on an unknown proportion of box a.

to media coverage of vaccine adverse events), and reporting of events that are unconfirmed or incompletely described [39]. The term "reporting efficiency" describes the proportion of occurrences of a specific type of event after administration of a particular vaccine that is actually reported to VAERS. Reporting efficiency is usually not well known, but has been found to be as high as 72% for OPV-associated paralytic poliomyelitis and as low as 1% for rashes occurring after MMR. Serious events and events occurring sooner after vaccination are more likely to be reported [40]. A US capture–recapture study found that reporting efficiency of intussusception following rotavirus vaccine approached 50%, although reports in both the medical literature and the media undoubtedly stimulated reporting [41].

Other limitations of passive surveillance systems include variability in quality and completeness of reports and reporter bias [39]. An attempt to standardize the reporting of adverse events has been provided by the Brighton Collaboration, an international voluntary collective of subject matter experts that develop standardized case definitions for adverse events [42]. In its current configuration, VAERS and most similar nationally based systems do not permit calculation of population-based incidence rates of adverse events. This is the result of incomplete reporting of adverse events, lack of knowledge of the total number of persons receiving a given vaccine or combination of vaccines, and lack of standard approaches to adverse event ascertainment.

Serious adverse events, including all deaths and hospitalizations, are often subject to further study. Follow-up often yields important clarifying information. For example, investigation of deaths reported to VAERS determined that the cause of death was significantly different from what was stated on the original report in nearly one-quarter of cases [43].

SRS data have been evaluated using descriptive epidemiologic approaches combined with medical judgment [44]. Typical methods used include review of individual cases (or related groups of cases) combined with the application of case definitions or classification criteria. Advanced signal detection or "data mining" techniques, which trace their origins to drug safety research [45], are also utilized as methods for identifying vaccine safety signals in need of further evaluation. The application of statistical significance tests or calculation of confidence intervals for vaccine safety data reported through SRSs should be undertaken with caution in consideration of the limitations of the data [39].

Despite their scientific drawbacks, vaccine safety monitoring systems have successfully detected early signals that were validated in subsequent studies. Reports identified oculorespiratory syndrome among influenza vaccinees from one Canadian manufacturer in one season [46]. Bell's palsy was also detected in recipients of a new Swiss intranasal influenza vaccine [47]. The Brazilian SRS detected higher rates of allergic adverse events with one brand of MMR after a mass campaign, subsequently leading to the product's withdrawal [48]. Equally important, such systems have provided reassurance of the safety of new vaccines such as the new meningococcal B and C vaccines in New Zealand and the UK [49].

In countries with limited resources, the WHO has encouraged the establishment of functional routine AEFI surveillance systems and support for NRAs as part of the Expanded Programme on Immunization (EPI) [50]. The primary focus is on detection of correctable programmatic errors such as injection site abscesses (suggestive of inadequate sterilization) and the development of a rapid response/assessment team for clusters of more serious events (e.g., toxic shock syndrome from contamination of vaccine vials or deaths from confusing other medications for vaccines). Both poliomyelitis eradication and measles mortality reduction programs have provided opportunities to pilot AEFI surveillance. In 2009, 147 of 193 national EPIs (76%) reported having AEFI monitoring systems [51]. Many of the countries without functional safety surveillance, particularly in sub-Saharan Africa, are resource poor.

Active surveillance and epidemiologic studies

Vaccine adverse events that are identified as safety concerns should be subjected to further clinical and epidemiologic analysis. Confirmation using data from a controlled study is usually required. Active surveillance generally requires unbiased collection of data regarding the incidence of the adverse event in question in both vaccine exposed and unexposed persons.

The Vaccine Safety Datalink (VSD) is the primary resource for vaccine safety hypothesis testing in the

USA. The VSD project is collaboration between CDC and several geographically diverse managed care organizations. These organizations have approximately 9 million enrollees, about 3% of the US population [16,52]. The VSD collects information on vaccination status, health outcomes, and demographic characteristics utilizing inpatient and outpatient claims data from participating facilities.

The general structure of the VSD, referred to as a large linked database (LLDB), allows assessment of medical events occurring in both vaccinated and unvaccinated persons in order to calculate an estimated relative risk of a health event after vaccination. The VSD plays an important role in conducting follow-up studies needed to answer urgent public health questions. One notable example was the timely confirmation of an association between intussusception and the first US-licensed rotavirus vaccine [17]. However, even LLDBs such as the VSD may not be sufficiently powered to detect extremely rare events such as GBS, whose vaccine attributable risk may be as rare as one per 1 000 000 [3,53]. Other LLDBs that have been used to conduct vaccine safety studies include the UK's General Practice Research Database [54] and the US Department of Defense's Defense Medical Surveillance System [55]. The UK, Denmark, Canada, and Vietnam have also used LLDBs for vaccine safety studies [56].

Although LLDB studies are typically used for hypothesis testing [17,52], they may also be used to conduct hypothesis generation or safety screening [57]. Applicable study designs include traditional cohort or case–control studies and the newer self-controlled case series analyses, in which each vaccinated person is acting as their own control [58]. Controlled vaccine safety studies using these databases have typically been conducted retrospectively, but newer methods allow the possibility of conducting prospective vaccine safety inquiries in near real time [57,59].

Other types of active surveillance used to conduct vaccine safety studies include hospital-based networks, such as the Canadian IMPACT system [60], which monitors AEFIs, vaccine failures, and selected infectious diseases in children. *Ad hoc* case–control studies can also be conducted to address vaccine safety issues with important public health implications [3,7,18,47,53], although such studies can be both labor and resource intensive.

Case studies

Influenza A H1N1 2009 vaccine and international public health response

In April 2009, a novel swine-origin influenza A H1N1 virus (2009 H1N1) was first detected along the USA–Mexico border, and by June 1, 2009, had spread through human-to-human transmission to 62 countries with 17 410 officially reported cases including 115 deaths [61]. In June 2009, the WHO declared the highest level of pandemic alert, and began coordination of 2009 H1N1 vaccine development [62].

Over thirty 2009 H1N1 influenza vaccines were developed and licensed in different countries within a time frame of approximately 3 months [63]. Distribution of the vaccines began in September 2009, and through June 2010 over 350 million doses were administered in more than 50 countries to differing target populations including healthcare workers, children, pregnant women, and individuals with certain underlying medical conditions. Because 2009 H1N1 influenza vaccines were licensed and produced over a relatively short time period and were administered to millions of people, the WHO advised all countries to conduct intensive monitoring for vaccine adverse events and coordinated exchange of safety information among public health and regulatory authorities in many countries [62]. Certain rare events were afforded special attention. There was particular concern about GBS, given the demonstrated causal relationship with the earlier 1976 US novel swine-origin influenza A (H1N1) virus vaccine [64].

In the USA, several federal vaccine safety surveillance systems were used. Existing systems, such as VAERS and VSD, were strengthened by increased staffing, improved databases, and enhanced reporting [65]. New systems included analysis of data from large health plans and state registries covering more than 10% of the US population, which allowed for linking vaccination data with healthcare outcomes data. A large population-based surveillance network called the Emerging Infections Program (EIP), a collaboration between the CDC and 10 state health departments, was used to identify possible cases of GBS. A special body, called the H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG), was formed with the specific purpose of conducting independent rapid assessments of 2009 H1N1 vaccine safety [65].

Through April 28, 2010, approximately 126 million doses of 2009 H1N1 monovalent vaccine were distributed in the USA. Preliminary analysis of VAERS data demonstrated a safety profile for 2009 H1N1 vaccine similar to that of seasonal influenza vaccine. Reporting rates were higher for 2009 H1N1 vaccine than for seasonal vaccine (82 and 47 reports per 1 million doses administered, respectively), likely because of efforts to increase VAERS reporting during the 2009 H1N1 vaccination campaign. No signals of unexpected AEFIs were detected [66, 67]. Preliminary data from the VSD rapid cycle analysis suggested an increased risk of Bell's palsy, but this finding was not substantiated in more detailed analyses. Other prespecified conditions did not show significant increases above expected incidence [66, 67].

A weak signal of GBS (adjusted rate ratio 1.77; 95% confidence interval 1.12–2.56) was detected through the EIP surveillance comparing GBS incidence in vaccinated and unvaccinated patients hospitalized through March 31, 2010 [68]. The population attributable risk of GBS was found to be 0.8 excess cases per 1 million vaccinations, which is comparable to the excess risk for some trivalent seasonal influenza vaccine formulations [53,69]. Five other surveillance systems conducted GBS surveillance but EIP was the only one that reported elevated relative risks that crossed the threshold for a signal. VSRAWG concluded that these safety results did not necessitate any immediate actions [70].

In June 2010, the WHO's Global Advisory Committee on Vaccine Safety concluded that the safety profile of the 2009 H1N1 vaccines was reassuring: most reported AEFIs had been non-serious and no unexpected safety concerns had been identified [71]. This example demonstrates how comprehensive vaccine safety monitoring can be conducted in the setting of public health emergency response, when vaccine is produced and distributed to millions of people within a short time frame and rapid postlicensure assessment of vaccine safety is warranted.

Quadrivalent human papillomavirus vaccine and syncope

The quadrivalent human papillomavirus recombinant vaccine (HPV4) was licensed in the USA in June 2006 for use among females aged 9–26 years to prevent precancerous lesions caused by HPV types 6, 11, 16, or 18 [72]. Because HPV4 was one of the first vaccines targeted to adolescents and the first vaccine against cervical cancer, its approval triggered extensive media and public attention, much of it concerned with assessment of postlicensure safety of HPV4. International prelicensure trials of the vaccine included approximately 21 500 patients and found that injection site reactions, fever, and nausea were reported more frequently after the vaccine compared with placebo. The rates of systemic and serious AEFIs were similar in both groups [73]. Postlicensure safety monitoring of HPV4 in the USA was conducted using VAERS [74,75]. VSD also conducted monitoring for such prespecified AEFIs as seizures, syncope, anaphylaxis, GBS, appendicitis, and venous thrombosis, using rapid cycle analysis [57,59].

The first comprehensive postlicensure assessment of HPV4 safety through VAERS was published in 2009. Approximately 12 000 VAERS reports following HPV4 vaccination were received by December 31, 2008, after over 23 million doses of the vaccine had been distributed in the USA. Overall, the safety profile of HPV4 vaccine was found to be consistent with prelicensure data: injection site reactions, dizziness, nausea, and headache were among the most commonly reported events. However, unlike in clinical trials, vasovagal syncope (i.e., fainting) was found to be the most frequently reported AEFI following HPV4. There were 1896 VAERS reports of syncope (reporting rate 8.2 per 100 000 doses distributed), 293 of them resulted in a fall, and 200 falls resulted in a head injury [76]. Preliminary VSD data were in agreement with VAERS findings and did not show elevated risks of any prespecified adverse event [77]. No overall increased risk was shown for syncope after HPV4 compared with other adolescent vaccines. This was consistent with VAERS data published in May 2008 that indicated increased reporting of syncope after all newly licensed adolescent vaccines (including HPV4, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and meningococcal conjugate vaccine), primarily among females aged 11–18 years [78]. The report noted that this age group has a higher background rate of syncope than other age groups. The CDC reinforced recommendations to providers to observe patients, seated or lying down, for 15 minutes after vaccination. Additionally, on June 9, 2009, the FDA approved a revised label for HPV4, in which information pertaining to syncope was included in the Warning and Precautions section, emphasizing that

Table 11.2 Characteristics of vaccine safety surveillance systems

General type of surveillance	Active	Passive (spontaneous reporting system)
Examples	VSD, GPRD, IMPACT	VAERS, CAEFISS, Yellow Card
Is population-based?	Yes	Yes
Primary objective	Hypothesis testing	Hypothesis generation
Can be used to calculate incidence of AEFI?	Yes	No
Can be used to calculate vaccine attributable risk of AEFI?	Yes	No
Sensitivity for rare event detection	Relatively low	Relatively high
Cost	Relatively high	Relatively low
Study designs	Cohort, case–control, self-controlled case series	Case series, advanced signal detection, or "data mining"

AEFI, adverse event following immunization; CAEFISS, Canadian Adverse Event Following Immunization Surveillance System; GPRD, General Practice Research Database; IMPACT, Immunization Monitoring Program-Active; VAERS, US Vaccine Adverse Event Reporting System; VSD, US Vaccine Safety Datalink.

healthcare providers and consumers should be alert that fainting may occur following vaccination with HPV4, sometimes resulting in falls and injuries, and recommending observation to prevent injury [79].

In May 2009, HPV4 became eligible for procurement by the United Nations Children's Fund and other United Nations agencies for use in national immunization programs [80]. By 2010, HPV4 vaccine was approved in over 100 countries and over 55 million doses were distributed globally as of December 2009 [73]. Additionally, in October 2009, bivalent recombinant HPV vaccine was licensed and is recommended by the WHO to be included in national immunization programs [81]. While data to date have not indicated the presence of serious or unexpected adverse events, given anticipated increased use worldwide, both HPV vaccines require ongoing and careful monitoring.

Conclusion

The importance of surveillance for vaccine safety is likely to continue to increase with ongoing licensure of new vaccines, implementation of expanded vaccine recommendations [82], and global immunization initiatives [83]. Vaccines will continue to be held to very high standards of safety. Recent prelicensure trials for second-generation rotavirus vaccines have involved nearly 70 000 subjects [84, 85]. Studies of this size can be costly and logistically difficult. Postlicensure surveillance systems, both active and passive, will continue to be responsible for monitoring rare, serious, and/or unexpected adverse events. The 21st century public health practitioner needs to understand the objectives and relative strengths and weaknesses of both primary types of systems. These are summarized in Table 11.2.

Vaccination policy decisions and communications with healthcare providers or the public related to vaccine safety issues should take into account available scientific surveillance data from all sources [86]. Clear communication of rare but potentially serious risks to an increasingly risk averse public may pose substantial challenges, but can be addressed through scientific principles of risk communication [87].

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Abbreviations

ACIP	US Advisory Committee on Immunization Practices
AEFI	Adverse Event Following Immunization
CAEFISS	Canadian Adverse Event Following Immunization Surveillance System
CDC	US Centers for Disease Control and Prevention
DMSS	Defense Medical Surveillance System
EIP	Emerging Infections Program
EPI	Expanded Programme on Immunization
FDA	US Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain–Barré syndrome
GPRD	General Practice Research Database
HPV4	quadrivalent human papillomavirus vaccine
IMPACT	Immunization Monitoring Program-Active
LLDB	large-linked database
MMR	measles, mumps, and rubella vaccine
MMWR	*Morbidity and Mortality Weekly Report*
MS	multiple sclerosis
NRA	National Regulatory Authority
OPV	oral polio vaccine
RRV-TV	tetravalent rhesus-based rotavirus vaccine
SAE	serious adverse event
SRS	spontaneous reporting system
TP	thrombocytopenia
VAE	vaccine adverse event
VAERS	US Vaccine Adverse Event Reporting System
VPD	vaccine-preventable disease
VSD	US Vaccine Safety Datalink
VSRAWG	Vaccine Safety Risk Assessment Working Group
WHO	World Health Organization