

Surveillance of adverse events following immunization in the late 2010s: an overview of the importance, tools, and challenges

O panorama da vigilância de eventos adversos pós-vacinação ao fim da década de 2010: importância, ferramentas e desafios

El panorama de la vigilancia de eventos adversos posvacunación al final de la década de 2010: importancia, herramientas y desafíos

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Abstract

Immunization is one of the most effective measures to protect individuals and the population against vaccine-preventable diseases. Vaccines are safe and effective products, but like any other drug they can cause adverse events, which tend to become more visible as the diseases are controlled, eliminated, or eradicated. This study analyzed activities in the surveillance of adverse events following immunization (AEFI) based on data from the scientific literature, websites of immunization programs and health and regulatory agencies, and the authors' expertise in the areas of immunizations and pharmacovigilance. With the increase in the number of vaccines in the basic immunization schedule and expansion of the population's access, it has become essential to establish an efficient surveillance system for AEFI in Brazil. However, underreporting of cases in Brazil and in other countries hinders the detection of AEFI, especially rare events. Constantly updated information on vaccines' risks and benefits allows immunization programs to provide rapid and clear responses to rumors of AEFI. This ensures the system's reliability, especially in the face of the growing antivaccine movement and the increasing influence of social media in public opinion.

Immunization; Immunization Programs; Postmarketing Product Surveillance

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Introduction

Immunization is one of the most effective public health measures to protect individuals and the population against vaccine-preventable diseases, and is responsible for saving millions of lives. Vaccines are safe and effective products, but like any other drug they can cause adverse events¹. An adverse event following immunization (AEFI) is any unwanted medical occurrence following vaccination, but which does not necessarily bear a causal relationship with the product and can be a symptom, disease, or abnormal laboratory finding².

Two factors increase the perception that vaccines need to be safer than other drugs or treatments: (a) vaccines are normally administered to healthy persons, and thus there is less tolerance of risk when compared to drugs administered to sick persons and (b) AEFI are gaining greater visibility in the population, since fewer people acquire the disease, thanks to consolidated immunization programs, with universal and sometimes mandatory recommendation, and with high sustained coverage of effective vaccines, which has led to the control, elimination, or even eradication of some diseases³.

With the reduction in the prevalence of vaccine-preventable diseases as the result of effective immunization programs, the surveillance and investigation of AEFI have become even more important for public health^{4,5}. There is greater concern about the quality and safety of vaccines, and more information is demanded by the general population and health professionals. In this increasingly complex situation, determining whether a vaccine is the cause of an AEFI or a mere temporal coincidence requires a detailed investigation and careful assessment of causality^{1,5}.

In Brazil, AEFI surveillance is conducted by the National Immunization Program (PNI, in Portuguese) within the Ministry of Health, the vaccine manufacturing laboratories, health professionals, and the user population. Notification and adequate investigation of AEFI allows the correct identification of the events actually caused by the vaccines, while ruling out coincidental events⁶. Surveillance of AEFI is part of pharmacovigilance, defined as the science and the activities related to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem⁷.

Records of AEFI in individuals vaccinated in the Brazilian public system are made available by the Ministry of Health, through the General Coordination of the PNI (CGPNI, in Portuguese), in the Information System on Surveillance of Adverse Events Following Immunization (SI-EAPV, in Portuguese)^{8,9}. The PNI launched the surveillance of AEFI in 1992, and compulsory notification was established on July 15, 2005¹⁰. For services in the private network, the Brazilian Health Regulatory Agency (Anvisa, in Portuguese) provides the National System of Notifications for Health Surveillance (NOTIVISA, in Portuguese)¹¹. The AEFI reported in Brazil thus come from these two sources. Pharmaceutical companies are also required to report AEFI involving their products, under Anvisa RDC n. 4/2009^{12,13}.

The lack of an effective response by health authorities to an event attributed to a vaccine can undermine the population's trust in immunization programs and lead to decreases in vaccination coverage and the resurgence of diseases⁵. A study that assessed trust in vaccines and hesitation to vaccination in Brazil interviewed 952 persons, of whom 16.5% expressed hesitation to vaccinate. Of the five most frequently cited reasons for hesitating to vaccination, three are related to doubts about vaccines' safety and efficacy¹⁴. To guarantee the public trust in national immunization programs, health professionals involved in the process should know the AEFI and be prepared to respond promptly to safety issues, thereby helping to avoid the propagation of fake news and rumors⁵.

In the current age, when fake news is everywhere and spreads with alarming speed, it is imperative to focus efforts on the rapid and mass dissemination of true and reliable news. Timely response to the public's concerns with vaccines' safety and effective communication increase the population's trust and preserve the immunization program's integrity⁸.

According to the study *Is Fake News Making Us Sick?*¹⁵, 67% of the interviewees showed that they believed in at least one inaccurate piece of information on vaccines. The majority of people who did not believe in vaccines' safety had seen negative news on social networks or instant message apps. The propagation of fake news through instant message apps led the Brazilian Ministry of Health to create a channel in 2018 to receive and investigate health news. Through WhatsApp, it is possible to refer a message received, which is analyzed and responded with an assessment of its veracity¹⁶.

The current study thus aimed to analyze surveillance activities for AEFI in Brazil and other countries, based on data published in the scientific literature, websites of immunization programs and health and regulatory agencies, and the authors' expertise in immunizations and pharmacovigilance.

Overview of AEFI surveillance in the world

According to published data, 48% of all people in the world live in countries without surveillance systems for vaccine safety⁹. The WHO Global Vaccine Action Plan (GVAP) identifies the establishment and strengthening of AEFI notification systems as a priority for immunization programs and defines the AEFI reporting ratio (number of AEFI per 100,000 live births) as a performance indicator to monitor the programs' progress⁹. In 1999, World Health Organization (WHO) created the Global Advisory Committee on Vaccine Safety (GACVS)⁴ with the aim of strengthening safety activities in vaccine use. The committee publishes reports on safety issues to support immunization programs.

Continuous assessment of vaccines' safety requires comparability between data from clinical trials and surveillance systems. This requires standardized case definitions for adverse events and guidelines for confirmation, registration, and presentation³. In 2000, WHO supported the creation of the Brighton Collaboration, a group that develops standard definitions of adverse events¹⁷. The group pioneered the guidelines for the collection, analysis, and standardized presentation of vaccine safety data³, and 61 guidelines had been developed as of the first half of 2019^{17,18}.

The U.S. Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) have used the Vaccine Adverse Event Report System (VAERS) for surveillance of AEFI since 1990¹⁸. This is a passive reporting system, mandatory for health professionals and manufacturers and accessible to citizens in general. Due to its wide access and accessible database, the VAERS has become a rich source of information on vaccine safety, but the reports should be viewed with caution, since they are not always verified by health professionals. The VAERS data are transmitted to the Uppsala Monitoring Center (UMC; Uppsala, Sweden), the WHO collaborating center for drug safety monitoring^{19,20}.

In Europe, the development of AEFI surveillance has been heterogeneous²¹. Currently, the European Medicines Agency (EMA) uses EudraVigilance, a system that facilitates online reporting of suspected drug-related adverse reactions and the analysis of these data, allowing timely detection of possible safety problems²². The information is available online to the entire population and is an important database for consulting suspected adverse reactions related to drugs, including vaccines.

AEFI surveillance has specificities in each country. Box 1 provides an overview of the similarities and differences between countries, allowing comparison of immunization programs and their respective surveillance systems.

Countries from different continents with varying degrees of socioeconomic development have public immunization programs, except the United States, where the immunization system is not totally financed by the government²³. In all the countries that were evaluated, AEFI surveillance is passive, while three countries also conduct active surveillance. Data management on AEFI is conducted by the immunization program, the health regulatory agency, or other areas of the Ministry of Health. In these different scenarios, access to the number of reported adverse events varies substantially, hindering the estimation of reports per 100,000 live births.

The AEFI reporting rate per 100,000 live births was proposed by the GACVS and adopted by the WHO SAGE (Strategic Group of Experts on Immunization) as an indicator to identify well-established AEFI surveillance systems. This indicator has been monitored globally and nationally. In 2017, 114 countries reported more than 10 events/100,000 live births, a significant increase (> 40%) compared to the data from 2010^{24,25}.

There was a movement in 2016 to improve the surveillance systems in developing countries, based on an initiative called the *Global Vaccine Safety Blueprint*. The objective was to assist developing countries in setting up work plans and developing surveillance systems. National committees were created to advise the drafting of standards and protocols for AEFI surveillance.

Box 1

Immunization programs and respective surveillance systems for adverse events in some countries.

Country	Estimated population *	Profile of immunization program	Vaccines in program portfolio	Implementation of AEFI surveillance system	AEFI surveillance system in use	Reporting (who reports?)	Management of AEFI surveillance system	Availability of AEFI data
Australia ^{66,67}	24.6 million	Public	16	1997	Passive and active	Health professionals: telephone; some states also provide websites. Consumers: completed form sent by fax, e-mail, or post; online form on the Therapeutic Good Administration (TGA) website	TGA. AusVaxSafety - NCIRS (National Center for Immunisation Research and Surveillance)	Periodic AEFI surveillance reports supplied since 2003 on the website
Brazil ^{19,68}	209.3 million	Public	18	1992	Passive	Mandatory for health professionals (National Immunization Program's Information System - SI-PNI) and industry (National System of Notifications for Health Surveillance - NOTIVISA). General public (NOTIVISA)	PNI: Information System on Surveillance of Adverse Events Following Immunization (SI-EAPV). Brazilian Health Regulatory Agency (Anvisa): NOTIVISA/ VigiMed	SI-PNI provides data to manufacturers after assessment and determination of causality

(continues)

Box 1 (continued)

Country	Estimated population *	Profile of immunization program	Vaccines in program portfolio	Implementation of AEFI surveillance system	AEFI surveillance system in use	Reporting (who reports?)	Management of AEFI surveillance system	Availability of AEFI data
Canada ⁶⁹	37.1 million	Public	19	1987	Passive (adults) Active (children)	Nurses, physicians, and pharmacists that work in immunization that manage AEFI. Manufacturers report directly to Ministry of Health. Active pediatric surveillance of selected AEFI (Immunization Monitoring Program ACTIVE – IMPACT)	Public Health Agency of Canada centralizes AEFI reports from health departments in provinces and territories, health professionals, and pharmaceutical industry	Four-monthly reports available (up to 2016) on the website of the Public Health Agency with overall data
China ⁷⁰	1.4 billion	Public	11	2005	Passive	Health services, vaccination clinics, agencies monitoring adverse drug reactions, vaccine manufacturers	Ministry of Health and Chinese Regulatory Agency (China Food and Drug Administration)	Analysis of national AEFI surveillance published monthly in the Bulletin of the National Immunization Program and distributed to the Chinese Centers for Disease Control and Prevention (CDC) and shared with the adverse events monitoring agencies

(continues)

Box 1 (continued)

Country	Estimated population *	Profile of immunization program	Vaccines in program portfolio	Implementation of AEFI surveillance system	AEFI surveillance system in use	Reporting (who reports?)	Management of AEFI surveillance system	Availability of AEFI data
Cuba ^{71,72}	11.4 million	Public	13	1996	Active (under 1 year) Passive (other age groups)	On a specific form, health professionals and companies	Center for State Control of Medicines, Teams and Medical Devices (CECMED)/ Ministry of Health	Periodic bulletins with general information
United States ⁷³	327.2 million	Private	12	1990	Passive	Health professionals, manufacturers, and public at large	Vaccine Adverse Event Reporting System (VAERS) is co-administered by Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA)	Public, through the VAERS Wonder system
Ghana ⁷⁴	29.4 million	Public	9	No information available	Passive	Health professionals, consumers, manufacturers	Expanded immunization program coordinates AEFI monitoring	Pharmacovigilance not available on the site
India ⁷⁵	1.35 billion	Public	11	1988	Passive	On online form (eCRF), health professionals and companies	Regulatory agency	Online bulletins with analysis of AEFI
Pakistan ^{76,77}	200.8 million	Public	9	2016	Passive	No information available	No information available	Pharmacovigilance not available on the site

(continues)

Box 1 (continued)

Country	Estimated population *	Profile of immunization program	Vaccines in program portfolio	Implementation of AEFI surveillance system	AEFI surveillance system in use	Reporting (who reports?)	Management of AEFI surveillance system	Availability of AEFI data
United Kingdom 78,79	66.5 million	Public	14	1964	Passive	Passive; public, manufacturers and health professionals. Each country has its reporting system, in England it's the Yellow Card (YC)	Medicines and Healthcare Regulatory Agency (YC)	EudraVigilance provides data to all of Europe

AEFI: adverse events following immunization.

* According data from the World Health Organization ⁸⁰.

As of 2016, Brazil was reporting more than 10 AEFI/100,000 live births, but the reporting rate was lower in the 2017 report, showing a troublesome scenario with worsening of the national AEFI surveillance system ^{24,25}.

Another difference between the countries is the number of vaccine-preventable diseases covered by the basic immunization schedule, as shown in Box 2. In addition to the number of vaccines, the supply of more reactogenic vaccines such as BCG and the combined diphtheria, tetanus, and whole-cell pertussis vaccine can affect the AEFI reporting rates.

Overview of AEFI surveillance in Brazil

In Brazil, the PNI was established by the Ministry of Health in 1973, launching a new phase in the history of public health policies with a focus on prevention and contributing to the reduction of morbidity and mortality from communicable diseases ²⁶. Immunization activities were already conducted in Brazil, but without overall coordination of their organization ²⁷.

The increase in the number of vaccines in the basic schedule over the years and expansion of the population's access required the establishment of an AEFI surveillance system. Following an international trend, in 1991 Brazil created its Technical Advisory Committee on Immunizations (CTAI, in Portuguese) as a technical and scientific advisory board for the PNI. The year 1991 also witnessed the elaboration of reporting forms, workflows, and standardized clinical protocols. Training of local and state immunization teams has been essential for increasing the system's sensitivity to capture cases of AEFI ⁶. The need to orient and standardize AEFI case reporting and investigation led the Brazilian Ministry of Health to publish (1998) the first edition of the *Manual on Epidemiological Surveillance of Adverse Events Following Immunization*, now in the third edition (2014) ⁶. Reporting has been online since 2000, through the SI-EAPV.

AEFI were included on the list of diseases of compulsory notification in 2005 ²⁸ and remain on the list today. The objective was to increase the detection of AEFI in public and private services and allow the adoption of appropriate control measures by government agencies. This inclusion made it mandatory for health professionals to report serious AEFI and deaths following immunization ²⁹.

Box 2

Availability of vaccines in the national immunization programs of some countries.

Vaccine	Brazil ⁸¹	United States ⁸²	Canada ⁵⁹	Australia ⁶⁰	United Kingdom ⁸³	Mexico ⁸⁴	China ⁷⁰	Ghana ⁸⁵	Cuba ⁶¹	Pakistan ⁷⁷	India ⁸⁶
BCG			*		**						
Hepatitis A			*		**						
Hepatitis B											
Triple bacterial (DTPw or DTPa or combined with Hepatitis B, IPV, and/or Hib)											
Haemophilus influenzae B											
Inactivated polio											
Oral polio	***					***	***				
Rotavirus											
Conjugated pneumococcal (7, 10 or 13-valent)											
Conjugated meningococcal (C or ACWY)											
Meningococcal B											
Influenza	**										
Yellow fever											
Triple viral (measles, mumps, rubella)											
Double viral (measles, rubella)	#	#	#	#	#	#			#		
Measles	#	#	#	#	#	#	#		#		#
Varicella (single or as MMRV)											
HPV											
Polysaccharide pneumococcal	**		*								
dTpa	**										
Herpes zoster			*	**	**						

Note: green = available; white = unavailable or not used by the country.

* Recommended in some provinces;

** Available for some specific population groups according to immunization strategy;

*** Sequential immunization (boosters and campaigns);

Diseases immunized with MMR vaccine or single measles vaccine.

The year 2008 witnessed the creation of the Inter-Institutional Committee on Pharmacovigilance of Vaccines and Other Immunobiological Products (CIFAVI, in Portuguese) by the Anvisa, CGPNI, and the National Institute for Quality Control in Health, Oswaldo Cruz Foundation (INCQS/Fiocruz) to promote coordinated activities among the components of the surveillance system³⁰.

Although AEFI surveillance with the PNI began in the early 1990s, the regulation of pharmacovigilance systems for vaccine producers only began in 2009, based on the *RDC n. 04/2009*¹³. The resolution was a major stride in post-marketing drug surveillance in Brazil, establishing pharmacovigilance activities for industry, ranging from compulsory reporting of AEFI related to its products to the development of a structure capable of monitoring the safety of marketed drugs³¹.

There is a global trend to harmonize pharmacovigilance standards between countries to allow joint data assessment. In 2016, Anvisa joined the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), which convenes regulatory authorities and pharmaceutical industry associations to discuss technical and scientific aspects related to drug registration³². Within five years after joining the ICH, Anvisa should adapt to a set of five ICH guidelines that standardize practices in pharmacovigilance and clinical research.

In addition to implementing a set of specifications to standardize drug registration known as the *Common Technical Document* (CTD), Anvisa will also be using the *Medical Dictionary for Regulatory Activities* (MedDRA)³³. Thus, the Pharmacovigilance standards and resolutions pertaining to Marketing Authorization Holder will be updated to deal with this new scenario.

The main difference between the pharmacovigilance activities by the PNI and Anvisa is the reporting source. While the PNI receives reports from health professionals in the public health system's vaccination spots, Anvisa receives reports from manufacturers, private vaccination services, and citizens in general, whether health professionals or not. However, reporting systems and forms are different for the general population, health professionals, and manufacturers, allowing broad uptake of adverse events. Private health services report AEFI to Anvisa^{6,10}. NOTIVISA is now being replaced gradually by VigiMed. The evolution of two parallel and complementary systems for detecting and recording AEFI, managed by Anvisa and PNI, will potentially improve the sensitivity, which is generally low in passive systems. Recent decades have seen the evolution of this system in Brazil (Figure 1).

Why investigate an adverse event following immunization?

Vaccines undergo a rigorous process in their registration by regulatory agencies, including various preclinical and clinical trials. However, the population studied in a clinical trial is selected, and all the factors are controlled. Besides, even a large clinical trial does not allow the inclusion of thousands of persons or the evaluation of special populations (such as elderly, pregnant women, and others). Thus, the maintenance of post-marketing vaccine surveillance through pharmacovigilance activities is essential for guaranteeing the vaccines' efficacy and safety¹⁸.

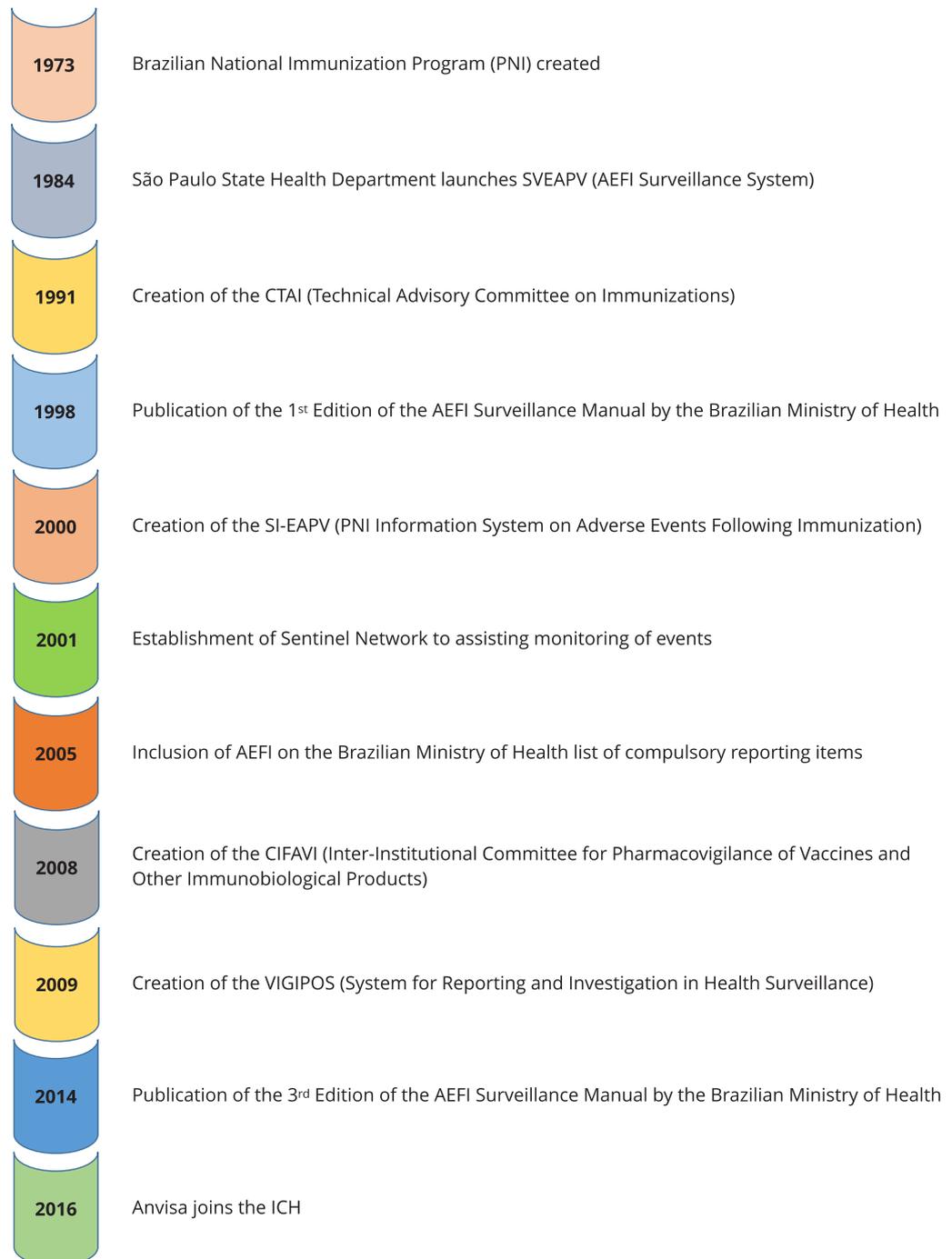
The reporting and investigation of AEFI contribute to the identification of rare or unexpected complications from immunizations, characterization of possible safety signs in vaccines, and identification of an increase in the rate of unexpected events. AEFI reports are captured by health information systems such as the SI-PNI and NOTIVISA.

According to the WHO, such systems should generate, compile, analyze, and summarize health-related data, allowing the data's use and communication. The reported data, together with other information such as health determinants and health systems performance, for example, serve as the basis for decision-making. The data are essential for monitoring and assessing health systems and also serve other purposes, such as support for patient and health unit management, monitoring of trends, and support for global reports, among others³⁴. Some well-documented episodes illustrate the role of AEFI surveillance in guaranteeing vaccines' safety, as described next.

Outbreaks of aseptic meningitis associated with the MMR (measles-mumps-rubella) vaccine applied in immunization campaigns in the Brazilian states of Bahia, Ceará, Mato Grosso, Mato Grosso do Sul, Piauí, and Rio Grande do Sul in 1997 and 1998 motivated the improvement of epidemiological surveillance of AEFI^{35,36}. Detailed investigation of these episodes suggested an asso-

Figure 1

Timeline in the evolution of the Brazilian National Immunization Program and adverse event following immunization (AEFI) surveillance systems.



Anvisa: Brazilian Health Regulatory Agency; ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

ciation with the use of MMR and supported the PNI in switching the vaccine manufacturer used in Brazil, guaranteeing the vaccine's safety and maintaining the health professionals' and population's trust in the system.

The rotavirus vaccine illustrates another situation in which AEFI monitoring was essential. Following registration of the first rotavirus vaccine (RotaShield; Wyeth Laboratories) in the United States in August 1998, studies showed its association with an increase of more than 30-fold in the risk of intussusception (a serious adverse event) in the week following the first dose³⁷, which led to the product's removal from the market by the manufacturer in 1999^{38,39}.

In Brazil, another rotavirus vaccine, RV1 (via a partnership between the Immunobiological Technology Institute – Bio-Manguinhos/Fiocruz – and the GlaxoSmithKline – GSK), was introduced in the PNI immunization schedule in March 2006 for children under one year of age³⁸. In May 2007, Mexico also included the RV1 vaccine in its immunization program. The vaccine is recommended in both countries from two to four months of age and should be initiated at 15 weeks of age at the latest. At the time of the introduction of RV1, Brazil and Mexico had about 6 million births per year, making it a favorable time for assessing a potential association between vaccination and increased risk of intussusception. A case-control study was thus conducted in 53 hospitals in seven states of Brazil and 16 hospitals in ten states of Mexico from August 2008 to August 2010⁴⁰.

The study showed an increase in the risk of intussusception in the first week after vaccination in Mexico, while in Brazil a possible risk was only observed in the first week after the second dose. These increased risks were translated as an excess of 96 cases of intussusception and five deaths in the two combined countries, figures that are exceeded by the benefits of vaccination, which prevents more than 80,000 hospitalizations and 1,300 deaths per year in the two countries⁴⁰.

The first dengue vaccine registered in Brazil (Dengvaxia; Sanofi-Pasteur) is another example of a product whose indication was changed due to post-marketing surveillance findings⁴¹. There are four dengue serotypes, and exposure to one does not confer immunity to the others. It is also known that a second infection with a different serotype increases the risk of developing a severe disease due to a phenomenon known as antibody-dependent enhancement (ADE)⁴². The vaccine protects against the four serotypes, but its estimated efficacy for individuals over nine years of age was 58%, 47%, 74%, and 83% for serotypes 1, 2, 3, and 4, respectively⁴³.

In November 2017, two years after the vaccine's registration, the manufacturer issued an alert on the increased risk of severe dengue in previously seronegative persons⁴². Follow-up data from clinical studies showed that individuals who were seronegative before vaccination, when vaccinated, developed non-protective antibodies against dengue, which could function like a primary infection and lead to the ADE phenomenon in case of exposure to the dengue virus and thus to a more serious clinical condition^{44,45}. Anvisa thus changed the vaccine's indication, recommending it only for persons with at least one prior infection by one of the dengue serotypes^{46,47}.

Another example of the importance of AEFI surveillance is the combination DTP-Hib vaccine, which began to be used in Brazil in 2002. The PNI received reports from some states of Brazil through the passive surveillance system for AEFI on the increasing frequency of adverse events related time-wise to this vaccine, mainly hypotonic-hyporesponsive episodes (HHE). However, the data were considered inconclusive and contradictory. Active surveillance was thus conducted, sponsored by the Ministry of Health, with the aim of assessing the incidence of HHE and other serious adverse events following the vaccine's administration⁴⁸.

A cohort of 21,064 infants was followed in the city of Rio de Janeiro for 48 hours after the application of DTP-Hib. HHE incidence was 1:1,744 doses (confirmed cases) and 1:1,495 doses (suspected cases, which includes the confirmed cases), while the incidence of seizures was 1:5,231 doses. No cases of apnea were detected. The results were comparable to those reported in the literature for this vaccine. This study allowed the PNI to respond quickly and robustly to the question raised by the passive surveillance system and allow the vaccine's safe and reliable use⁴⁸.

This study was used as the basis for another, conducted from 2000 to 2013 in the city of Araquara, São Paulo State, with the aim of assessing the sensitivity of a passive surveillance system. The study used HHE incidence and seizures as sentinel events, considering the reported rate in the active surveillance study as the gold standard. The authors calculated the sensitivity of the passive

surveillance system at 71.9% and 78.9% for HHE and seizures, respectively, and concluded that a well-conducted passive surveillance system can be a good thermometer for changes in vaccines' safety profile ⁴⁹.

How to investigate an AEFI?

The essential elements in the AEFI concept are temporality and biological plausibility, which makes the case definition for surveillance purposes operationally simple and objective. While this concept maximizes the sensitivity for capturing events potentially associated with the vaccine, it also requires investigation of these cases to determine whether the vaccine's implication is more likely than alternative hypotheses ³⁹. For example, the RotaShield rotavirus vaccine was removed voluntarily from the U.S. market by the manufacturer less than a year after its introduction, when data from AEFI reports showed an additional risk of 1 to 2 cases of intussusception per 10,000 infants vaccinated ³⁹.

The main objective of investigating an AEFI is to determine whether the vaccine/vaccination was responsible for the event. Data collection is crucial to the investigation and includes clinical, epidemiological, and laboratory data, in addition to information on the product that was administered. This requires the involvement of teams from the vaccination rooms, epidemiological surveillance, patient care, reference laboratories, and central management (PNI).

In addition to data collection, it is often necessary to collect clinical samples. If this is not done at the right time, it can compromise or even entirely prevent the investigation's conclusion. Serious adverse events or "clusters" of AEFI should be investigated immediately in such cases, and time is essential for the investigation's success. A sample that is not collected at the right time, not stored adequately, or not transported correctly can jeopardize the process.

Box 3 lists the necessary information for satisfactory investigation of an AEFI, allowing to establish causality.

Box 3

Information that should be collected during investigation of an adverse event following immunization (AEFI).

VARIABLES		DESCRIPTION
1	Demographic data	Age, sex, address, contact info
2	History of current disease	Symptoms, signs, timeline, date of onset and duration, treatment, diagnosis, and outcome
3	Family history	Diseases in family members (genetic, autoimmune, etc.)
4	Personal disease history	Adverse events with previous doses of the vaccine, allergies, underlying diseases, medications
5	Vaccination history	Vaccine(s) received, with batch number, number of doses received, vaccination date, place of administration (especially vaccines received in the 30 days prior to the event and previous doses of the vaccine suspected of the AEFI)
6	Laboratory results	Test results (laboratory, imaging, etc.) performed for investigation of the event
7	Outcome	Information on death certificate and autopsy report (when applicable)
8	Vaccine(s) suspected of the AEFI	Batch number, manufacturer, information on vaccine's storage, whether alterations were detected by local team, place of vaccination (name of health unit), information on similar cases with same batch or same health unit
9	Quality of suspected vaccine(s)	Information on quality control of suspected vaccine(s)

Source: adapted from World Health Organization ⁸⁷.

When a suspected case is detected, the health unit should promptly notify the epidemiological surveillance system, which should launch an investigation within 48 hours. From there onward, with the case already entered into the SI-EAPV database, it is referred to the regional coordinating bodies and from there to the states. The initial data inserted into the system are updated as new information is obtained ⁶.

According to *Ruling n. 204/2016*, every actively working health professional has the obligation to report a case of AEFI to the respective administrator under the Brazilian Unified National Health System (SUS, in Portuguese), even if the event occurred in a private healthcare establishment ²⁹.

The investigation of an AEFI includes data collection, case classification according to severity (serious, not serious), intensity (mild, moderate, intense), predictability (whether or not described in the package insert), and assessment of causality (consistent, indeterminate, coincidental, or non-classifiable). Adverse events also need to be coded in medical terms to facilitate comparison of cases. Currently, the most widely used terminology is the MedDRA, created in the late 1990s by the ICH ³³. The terminology is standardized, complete, and highly specific, facilitating international exchange of regulatory information ³².

The most important and difficult stage in the investigation of an AEFI is the assessment of causality, whose objective is to determine whether there is a cause-and-effect relationship between the vaccine/vaccination and AEFI. This analysis is based mainly on the temporal relationship between the vaccine's administration and the event, medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathology findings, mechanism of action), and probability or exclusion of other causes. All data on the case should be available in this stage ⁵⁰.

In 2012, the Council for International Organizations of Medical Sciences (CIOMS) and WHO revised the classification of specific causality for AEFI, now currently in use in Brazil by the PNI ^{6,51}. Standard case definitions facilitate investigation of AEFI. In 2004, the Brighton Collaboration published its first case definitions, recommended by the American Academy of Pediatrics, CIOMS, EMA, FDA, and other organizations ⁵².

One of the adverse events with a case definition by the Brighton Collaboration is yellow fever vaccine associated acute viscerotropic disease (YFV-AVD). A working group was launched in 2008 to optimize the identification of clinical cases referred for laboratory investigation. The objective was to develop a standard definition of suspected YFV-AVD cases, with guidelines for data collection, analysis, and presentation, facilitating comparison between countries ⁵³. YFV-AVD is a serious and highly rare adverse event, defined as an acute multiple organ dysfunction following vaccination. Severity varies from a relatively mild multisystemic disease to severe multiple organ failure and death. The causal relationship between YFV and AVD can only be confirmed by genetic sequencing of the vaccine virus in the patient's clinical specimens, because clinical symptoms are similar to those observed in infection with the wild-type virus ⁵³. This is a good example of an AEFI in which early investigation is essential. For the diagnosis to be made, blood samples need to be drawn promptly at the onset of symptoms, and in case of death, visceral samples should also be obtained. Timely sample collection is necessary to meet the criteria for case definition and confirmation. The healthcare team's difficulty in collecting and referring samples to the reference laboratories means that many of these cases are classified as suspected, without the possibility of ruling out causality, which can undermine the population's trust in the vaccine.

Another example of the importance of standard definitions involves cases of anaphylaxis, an acute hypersensitivity reaction with multiple organ involvement which can be severe and present risk of death. The reaction can occur after exposure to allergens from a variety of sources, including aeroallergens, foods, drugs, immunizations, and insects. The definition of anaphylaxis can be difficult, and if based only on clinical judgement, there may be discordant diagnoses between physicians. Thus, the case definition of anaphylaxis by the Brighton Collaboration is important, since it allows standardization, comparison, and monitoring of tendencies between cases ⁵⁴.

In Brazil, the PNI also developed standard protocols for the investigation of some adverse events, such as YFV-AVD, yellow fever vaccine associated acute neurological disease (YFV-AND), and acute flaccid paralysis following attenuated oral polio vaccine. These protocols orient the identification of suspected cases, specimen collection for specific tests, sample flow, and final case classification, supporting local surveillance services in conducting the investigation process ⁶.

Difficulties and challenges

AEFI surveillance is an essential activity for guaranteeing the safety and reliability of vaccines in the post-marketing phase. However, as explained above, there are numerous difficulties in successfully performing this task.

Passive AEFI surveillance has been the most common form of post-marketing surveillance of AEFI. The main objective of passive surveillance is prior detection of unknown events or any alterations in the reporting profile of known AEFI⁵⁵. Due to their national reach, passive systems are often the only available methods for monitoring extremely rare AEFI.

However, passive systems have limitations, such as underreporting of cases, reports of unconfirmed temporal and diagnostic associations, data with biases (e.g., serious adverse events are probably more reported than non serious ones), and difficulty in estimating incidence rates⁵⁵.

Underreporting of AEFI occurs both in Brazil and in other countries. A Brazilian study in 2018 described the AEFI in the SI-EAPV database (a passive surveillance system) which included 24,732 reports from 2,571 municipalities (counties), representing fewer than half (46.2%) of all Brazilian municipalities reporting at least one AEFI¹⁰. A study in the Czech Republic with active AEFI surveillance recorded 175 AEFI after routine vaccination of children, with a calculated AEFI rate of 209/100,000 doses of vaccine. This was much higher than the official AEFI rate obtained by passive surveillance by the agency in charge of recording AEFI in that country (34/100,000 recorded doses) during the same period, thus revealing the existence of underreporting⁵⁶.

A study in Albania assessed health professionals' perception of AEFI surveillance and barriers to case reporting. A questionnaire was applied to primary care personnel (n = 102). Of the respondents, 70.5% said they had already treated an AEFI, but fewer than half of these had reported the case. The main reasons for non-reporting were lack of interest, unclear definitions of AEFI, and lack of knowledge on what is and is not notifiable⁵⁷.

To improve the AEFI detection, some countries have used new tools to conduct active surveillance. In Australia, SmartVax is a vaccine safety monitoring system that uses SMS-type messages for case follow-up. Three days after immunization, messages are sent to the parents or guardians of vaccinated children, asking if there had been any "reaction" after the vaccine. The response is yes or no only, and if the users replies "yes", two more messages are sent asking for more information while an alert is generated in the system, referring the case for investigation⁵⁸.

Various challenges arise in the process of investigating an AEFI, and the first difficulty is that emergency services need to be sensitive to the possibility of an adverse event. During vaccination campaigns, it is easier to raise the teams' awareness of the suspicion of an AEFI, but in routine immunization many cases may go unnoticed by the healthcare teams. This is a weakness in the passive reporting system, so that many countries like Australia, Canada, and Cuba have implemented active surveillance systems, with the main focus on children^{59,60,61}.

Another difficulty in the investigation process is differential diagnosis, essential for establishing the causality of an AEFI and to rule out other possible causes of the reported signs and symptoms⁶. For example, in the case of a neurological syndrome (meningoencephalitis) following yellow fever vaccine, in addition to investigating the yellow fever virus, other causes of bacterial and viral meningitis need to be investigated and ruled out to allow confirmation of a case of YFV-AND.

In Brazil, the state level in the coordination of immunizations is responsible for analyzing, classifying causality, and closing cases of AEFI, validating the data from the municipalities (counties). Meanwhile, the federal level analyzes and validates reports from the states after closure, consulting the CIFAVI and other technical support groups when necessary⁶.

Case closure is often impossible, because many reports of AEFI are incomplete and lack essential information for assessing the case, such as the vaccine batch, date of vaccination, timeline of the symptoms, and others. In a study in India, 37% of the deaths reported as AEFI were closed as unclassifiable, that is, information was missing to analyze causality⁶². In the study cited above on AEFI in the SI-EAPV, of the 24,732 cases reported in Brazil, only 1,622 were closed by the end of the study period, as only 6.6% of the cases had their investigation concluded¹⁰. These data corroborate previous studies, suggesting data quality problems, which can include typing errors, missing fields on the form, and flaws in the information flow, hindering correct analysis of the reports^{63,64}.

Adverse events associated with immunization errors are just as relevant⁶. Failures in the transportation, storage, handling, and application of vaccines and identification of contraindications and precautions may not result in adverse events, but they can contribute to their occurrence. Vaccination campaigns administer more doses than routine immunization and are concentrated in time and with the mobilization of extra human and physical resources and may thus be more prone to immunization errors, which can only be detected via investigation of adverse events.

Another challenge for immunization programs is the relationship with the media and the community in cases of adverse events, which cause commotion in society. A solution to facilitate dealing with these situations in case of large-scale vaccination campaigns is to establish a crisis management plan, specifying procedures in the management of AEFI cases if they occur⁶². The plan should include a communication strategy, identifying a focal point for contact with the press, community, and social medias. Ideally, professional journalists in a press advisory board should coordinate this activity in order to deliver clear messages and mitigate the spread of rumors⁶⁵.

Conclusions

AEFI surveillance is essential for guaranteeing the maintenance of vaccines' efficacy and safety.

With the current resurgence of vaccine-preventable diseases, the growth of antivaccine movements, and social medias' growing influence on public opinion, it is extremely important to have constantly updated and comprehensive information on vaccines' safety, allowing immunization programs to produce rapid and clear responses to adverse events.

The lack of an effective surveillance system can cause incalculable damage to an immunization program's credibility and lead to major reductions in vaccination coverage, which is difficult to recover. Health professionals should be aware of their important role in this process, since they are the portal of entry for information on vaccines' safety.

Brazil is experiencing the resurgence of diseases like measles and yellow fever. Collective effort is crucial for overcoming the discredit and fear of vaccines and return to the ideal vaccine coverage levels. Information is the best way to combat fear. AEFI surveillance is an essential component of generating the necessary evidence for guaranteeing safe and effective vaccines for use in Brazil.

Structured activities in the surveillance of adverse events to protect the public and safeguard the immunization programs are consolidated in systems specifically dedicated to provide rapid and effective response to reports of real or presumed unwanted effects from the application of vaccines. Despite important strides, there is much room for improvement, especially in reporting and investigating these events.

Contributors

All authors contributed to the conception, writing, revision, and approval of the final version.

Conflict of interest

The authors work for Bio-Manguinhos/Fiocruz, a public laboratory that produces various vaccines for the PNI.

Additional informations

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Resumo

A vacinação é uma das ações mais efetivas para proteger o indivíduo e a população contra doenças imunopreveníveis. Vacinas são produtos seguros e eficazes, porém, como qualquer outro medicamento, podem causar eventos adversos, que ganham maior visibilidade na medida em que as doenças são controladas, eliminadas ou erradicadas. Este trabalho analisou as ações de vigilância de eventos adversos pós-vacinação (EAPV) com base em dados da literatura científica e sites de programas de imunizações, agências reguladoras e de saúde, além da expertise dos autores nas áreas de imunizações e farmacovigilância. Com o aumento do número de vacinas no calendário básico e a ampliação do acesso da população, tornou-se fundamental o estabelecimento de um sistema eficiente de vigilância de EAPV no Brasil. Entretanto, a subnotificação de casos no Brasil e em outros países dificulta a detecção de EAPV, principalmente os raros. Informações sempre atualizadas sobre o benefício/risco das vacinas permitem que programas de imunizações deem respostas rápidas e claras aos rumores de EAPV. Isso garante a confiabilidade no sistema, ainda mais diante do crescente movimento antivacínista e a influência cada vez maior das mídias sociais na opinião pública.

*Imunização; Programas de Imunização;
Vigilância de Produtos Comercializados*

Resumen

La vacunación es una de las acciones más efectivas para proteger al individuo y a la población contra enfermedades inmunoprevenibles. Las vacunas son productos seguros y eficaces, sin embargo, como cualquier otro medicamento, pueden causar eventos adversos, que tienen mayor visibilidad según se controlen, eliminen o se erradiquen las enfermedades. Este trabajo analizó las acciones de vigilancia de eventos adversos posvacunación (EAPV), basándose en datos de la literatura científica y sitios web de programas de inmunizaciones, agencias reguladoras y de salud, además de la expertise de los autores en las áreas de inmunizaciones y farmacovigilancia. Con el aumento del número de vacunas en el calendario básico y la ampliación del acceso de la población, se hizo fundamental el establecimiento de un sistema eficiente de vigilancia de EAPV en Brasil. Sin embargo, la subnotificación de casos en Brasil y en otros países dificulta la detección de EAPV, principalmente, los raros. Informaciónes siempre actualizadas sobre el beneficio/riesgo de las vacunas permiten que programas de inmunizaciones proporcionen respuestas rápidas y claras a los rumores sobre EAPV. Esto garantiza la confianza en el sistema, incluso más aún ante el creciente movimiento antivacunas y la influencia cada vez mayor de los redes sociales en la opinión pública.

*Inmunización; Programas de Inmunización;
Vigilancia de Productos Comercializados*

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