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# Surveillance of adverse effects following vaccination and safety of immunization programs

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## ABSTRACT

The aim of the review was to analyze conceptual and operational aspects of systems for surveillance of adverse events following immunization. Articles available in electronic format were included, published between 1985 and 2009, selected from the PubMed/Medline databases using the key words “adverse events following vaccine surveillance”, “post-marketing surveillance”, “safety vaccine” and “Phase IV clinical trials”. Articles focusing on specific adverse events were excluded. The major aspects underlying the Public Health importance of adverse events following vaccination, the instruments aimed at ensuring vaccine safety, and the purpose, attributes, types, data interpretation issues, limitations, and further challenges in adverse events following immunization were describe, as well as strategies to improve sensitivity. The review was concluded by discussing the challenges to be faced in coming years with respect to ensuring the safety and reliability of vaccination programs.

**DESCRIPTORS:** Vaccines, adverse effects. Immunization Programs. Clinical Trials, Phase IV as Topic. Product Surveillance, Postmarketing. Review.

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## INTRODUCTION

Vaccines have contributed to the effective control of countless infectious diseases in recent decades, having had expressive impact on child morbidity and mortality.<sup>16,86,87,94,95,104</sup> Their good performance in terms of cost-effectiveness and safety has made vaccination a mandatory component of public health programs.<sup>16,19</sup> Evaluation of this performance is based on the vaccine’s coverage, equity of access, and safety.<sup>19,31,111</sup>

The success of immunization programs creates a paradoxical situation in developed countries: as the perception of risk associated with immunopreventable diseases decreases, the fear of adverse effects following immunization (AEFI) increases.<sup>43</sup> This can reduce compliance with vaccination, allowing for the reemergence of controlled diseases.<sup>20,21,23,38,48,56,83,94</sup>

Expectations with regard to vaccine safety are high, given that they are administered to healthy individuals.<sup>23,37,68</sup> However, like other pharmaceutical products, vaccines are not entirely free of risk,<sup>22,38</sup> which makes safety one of the key elements in ensuring high adherence to immunization programs.<sup>23</sup> Immunoprophylactics contrast with other classes of drugs that have alternative therapeutic regimens, since, with the exception of the poliomyelitis vaccine, little is available in terms of alternatives.<sup>23</sup> Although precise risk estimates are

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lacking, data from the literature indicate that the safety of vaccines is significantly higher than that of other pharmaceutical agents.<sup>107</sup>

Concerns with vaccine safety and with maintaining high vaccine coverage have led a number of countries with different health care service structures to create systems of surveillance for adverse effects following immunization (SAEFI).<sup>2,46,58,61,68,70,74,97,114</sup> Brazil, which has one of the most successful immunization programs in the world, created a nationwide passive SAEFI system in 1998.<sup>76,106</sup>

Given their recent implementation, and the fact that such systems are not yet adopted in most countries,<sup>36</sup> there is very little knowledge of the SAEFI's goals, strategies, and requirements in terms of adaptation to the peculiarities of health care systems in different countries. The aim of the present review was to analyze certain conceptual and operational aspects of SAEFI systems.

A review of the literature published between 1985 and 2009 in the MEDLINE/PubMed database using the key-words "adverse effects following vaccine," "adverse effects following vaccine surveillance," "post-marketing surveillance," "safety vaccine," and "Phase IV clinical trials" was carried out. Articles in Portuguese and English, available in electronic format, and which focused on concepts, characteristics, attributes, and limitations of SAEFI systems were included, as well as on the Brazilian SAEFI experience. Articles published prior to 1985 which were considered as relevant were included and excluded articles on specific types of AEFIs.

## RELEVANCE OF AEFIS TO PUBLIC HEALTH

An AEFI is defined as any severe and/or unexpected adverse sign or symptom occurring after vaccination. It may be associated with the vaccine, when it is caused by it or triggered by any of its inherent properties, even when administered correctly. AEFIs can be the consequence of program errors – related to inadequate vaccine preparation, handling or administration – or can be coincidental events – those occurring after vaccination but whose association with immunization is temporal rather than causal.<sup>109</sup> The risk of AEFIs has been documented since the earliest days of smallpox vaccination.<sup>35</sup> The first piece of legislation aimed at ensuring the safety of immunobiologicals was probably that enacted in 1901 in the United States following an incident in St. Louis, Missouri, in which 13 children died after receiving anti-diphtheria serum contaminated with *Clostridium tetani*.<sup>53</sup> The frequency and severity of AEFIs associated with smallpox vaccination justified the suspension of vaccination in industrialized countries even before the eradication of the disease was declared.<sup>67</sup>

In the 1970's, the wide publicity given to AEFIs associated with the *pertussis* component of the whole-cell DPT vaccine triggered a decrease in coverage of this vaccine and the reappearance of diseases prevented by this vaccine in countries like Japan and Sweden.<sup>3,21,38,48,94</sup>

A similar situation occurred following a study by English researchers<sup>103</sup> reporting an association between the measles vaccine and autism, which has failed to be confirmed by subsequent studies.<sup>51</sup> This report led to a decrease in measles vaccine coverage and the reappearance of measles in England.<sup>59,95</sup>

Poliomyelitis epidemics associated with poliovirus derived from the oral vaccine have triggered a discussion of changes in immunization strategies.<sup>41, 49, 89</sup>

The incidence and intensity of AEFIs vary according to the characteristics of the vaccine, vaccinee, and vaccination mode. These are often mild, rapidly self-limiting disorders; however, more severe reactions do occasionally occur. The mechanisms of these reactions are not fully understood.<sup>110</sup>

Given the relevance of immunobiologicals to public health, the World Health Organization (WHO)'s Department of Immunization, Vaccines, and Biologicals implemented the Immunization Safety Priority Project in 1999. In 2003, a wide-ranging system was implemented to ensure the safety of vaccines administered as part of national immunization programs.<sup>36</sup>

## VACCINE SAFETY EVALUATION

Vaccines are pharmacological products that contain one or more immunizing agents in different biological forms, and may include components of culture media or of the cell cultures used in the production process, preservatives, stabilizers, and antibiotics.<sup>110</sup>

The vaccine licensing process requires an evaluation of the product's safety and efficacy by means of pre-clinical and clinical trials (phases I to III).<sup>26,72,78,108</sup> Among the limitations of these trials are the limited follow-up period, small number of subjects, and rigid inclusion criteria, all of which hinder the identification of rare but potentially relevant AEFIs.<sup>7,26,54,100</sup> Only after the commercialization and widespread use of a vaccine is it possible to determine its associated AEFI spectrum and to investigate putative risk groups and risk factors.<sup>26,28</sup>

AEPI surveillance,<sup>99</sup> also known as phase-IV or post-marketing surveillance studies,<sup>28,58</sup> is the recommended instrument for monitoring the safety of vaccines after commercial release. SAEPI has its origins in pharmacosurveillance, in the 1960's, after the epidemic of phocomelia associated with use of thalidomide during pregnancy in a number of countries.<sup>69,71,111</sup>

Instruments and measures aimed at promoting vaccine safety include, in addition to SAEFI, procedures for quality control and compliance with specifications; evaluation of technologies applied to vaccination, such as vaccine quality, storage, handling, administration, and needle and vial disposal; identification and management of risks related to immunization, creating mechanisms for AEFI monitoring and quick response alongside the community in case of AEFIs raising doubts as to the safety of national immunization programs.<sup>27,36</sup>

## GOALS AND ATTRIBUTES OF SAEFI SYSTEMS

SAEFI systems are aimed at providing information that allow for continuous assessment of the safety of a given vaccine in the studied population in a timely manner.<sup>99</sup> Moreover, such systems should provide users with up-to-date information on adverse effects and contraindications,<sup>58</sup> as well as subsidy to the development of procedures aimed at ensuring the safety of immunization programs.

Foremost among the aims of SAEFI systems are the following:

- to detect, correct, and prevent program errors;
- to identify problems with specific batches or brands of vaccine;
- to alert the population about AEFIs falsely attributed to a given vaccine due to coinciding events;
- to maintain the community's trust in the program by responding adequately to increased perception of vaccine-associated risk;
- to investigate rare AEFIs not identified in studies preceding the vaccine's release as well as delayed reactions to the vaccine;
- to monitor increases in frequency of known AEFIs;
- to identify risk factors associated with AEFIs; and
- to identify signs of potential AEFIs that are unknown or not fully understood.<sup>36,58</sup>

Simplicity, low cost, sufficient representativeness to prevent unwarranted decisions, and the ability to identify AEFI cases (sensitivity) and to distinguish them from events not associated with immunization (specificity) are considered as necessary for SAEFI systems to achieve good performance. To this, we add the ability to fulfill the stages predicted by the SAEFI system in a timely manner, aiming at the adoption of

intervention measures, whenever necessary.<sup>52,99</sup> The latter attribute is of particular importance in situations that involve serious risk to the health of the population, such as the outbreak of Guillan-Barré syndrome taken place in the United States in 1976, associated with mass vaccination against the H1N1 influenza virus,<sup>91</sup> or the identification of overly reactogenic vaccine batches, which should be recalled immediately.<sup>92</sup>

The minimal required information for the proper functioning of a SAEFI system are: type of vaccine, date of administration and onset of clinical manifestations; type of health service and characteristics of the health care unit in which the vaccine was administered, characteristics of the vaccinee, and clinical manifestations. In case of hospitalization, it is also necessary to obtain information on duration, conditions at discharge, and conduct regarding the continuity of the vaccination schedule. Information on co-morbidities, personal and family morbidity history, prior history of AEFIs, and type of adverse reaction.<sup>99</sup>

## TYPES OF SAEFI SYSTEMS

SAEFI systems may be passive or active. Passive systems are most often used, and are based on voluntary notification of adverse events by health workers or by the patient or care giver.<sup>105</sup> This type of system is the simplest and least expensive alternative, and their wide population base allows for the identification of rare events and of the safety profile of vaccines in the post-licensing period. On the other hand, this approach has low sensitivity and provides imprecise risk estimates when using as a denominator the number of doses of vaccine distributed or administered, which is an imperfect definition of the exposed population.<sup>58,114</sup>

Given the limitations of clinical trials in identifying rare events and the low sensitivity of passive SAEFI systems, a number of developed countries have implemented active surveillance systems.<sup>42,a</sup> Active SAEFI systems monitor the vaccination activities of all individuals in a defined population, which allows one to link postvaccination clinical manifestations to the type of vaccine administered.<sup>6</sup> This reduces underreporting and allows for more precise estimates to be made of the incidence of AEFIs.<sup>24</sup>

Among the less complex alternatives for implementing an active SAEFI system are the Canadian Immunization Monitoring Program Active (IMPACT), established in 1990. IMPACT is a partnership between the Canadian Society of Pediatrics and 12 pediatric centers distributed across the country, which are responsible for 90% of tertiary care admissions.<sup>a</sup>

<sup>a</sup> Canada. Health Canada. Immunization and Respiratory Infections Division – Vaccine safety. Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) [Internet]. 2010. [cited 2010 Oct 25]. Available from: <http://www.phac-aspc.gc.ca/im/vs-sv/caefiss-eng.php>

Another simple alternative was adopted in an area in the city of Rio de Janeiro, Southeastern Brazil, to evaluate severe adverse effects following DPwT/Hib vaccination after the inclusion of this vaccine in routine use in 2002. This program studied a cohort of children enrolled in 16 primary health care units. These units were part of the municipal health care network of the city of Rio de Janeiro, and therefore comprised a very well-defined population.<sup>76</sup>

A more complex active SAEFI strategy is the analysis of information from cohorts of individuals within delimited areas or areas covered by the same health care providers. These providers have large databases consisting of electronic patient files (EPFs) linked to electronic immunization registries (EIRs).<sup>20</sup> The data stored in these databases include information on vaccination, intercurrent clinical events, and other data on the target population. Real-time data entry reduces underreporting and recall bias<sup>24</sup> and allows for more precise denominators to be obtained for risk estimation. However, limitations of this strategy include high cost, representativeness (which may be low), and difficulty to identify very rare events among the small populations included in the EIRs.<sup>20,73,114</sup>

One of the earliest instances of such a strategy is the Datalink project,<sup>20</sup> begun in 1991, as an initiative of the Centers for Disease Control and Prevention (CDC), which covers eight different regions of the United States and approximately 650 thousand children under the age of six years (3.5% of children in this age group).<sup>33</sup>

In addition to minimizing mistakes and underreporting in AEFI notifications, the articulated use of EIRs and EPFs may subsidize the proper indication of special immunobiologicals for children and of vaccines for adults. This procedure requires knowledge of the vaccination history, risk factor profile, and overall health status of both the subject and his or her contacts.<sup>32,44</sup> However, the use of such electronic systems requires the adoption of rigid privacy policies.<sup>73</sup>

Since 1992, there exists in Italy a program linked to the SAEFI system called Green Channel, which is aimed at preventing AEFIs in individuals with prior history of such events or who have contraindications for beginning or continuing vaccination regimens.<sup>113</sup>

#### **STANDARDIZATION OF CASE DEFINITIONS IN SAEFI SYSTEMS**

It is possible to establish the safety profile of a given vaccine, i.e., to identify a combination of AEFIs, based on SAEFI data, for only a subset of adverse events – such as fever and local reactions – are common to the

large majority of vaccines. For each vaccine, there is a particular combination of AEFIs.<sup>12</sup>

Methods exist for analyzing SAEFI data that, by relying on proper statistical methods, are able to characterize the safety profile of vaccines by comparing similarity indexes. This allows one to identify the reactogenicity profiles of different vaccines using data pertaining to the numerator and comparing the distribution and types of AEFI.<sup>18</sup>

Given the difficulties in standardizing AEFI definitions, countries such as the United States and Australia follow the directives adopted by pharmacological surveillance and adopt classifications based on severity criteria. This classification considers as severe all adverse events leading to death, risk of death, permanent or significant disability or hospitalization.<sup>70,96,101</sup>

In order to establish a vaccine's safety profile, it is essential that the definition of cases of each AEFI be standardized, since this allows for data comparability and increases the specificity of surveillance.<sup>9</sup>

The international Brighton Collaboration<sup>b</sup> (BC) was set up under the auspices of the CDC, WHO, the European Research Program for Improved Vaccine Safety Surveillance (EUSAFEVAC), and specialists from a number of countries in 2000.<sup>9</sup> This group supports the creation of technical groups interested in developing and improving AEFI case definitions, and facilitates the distribution and quality assessment of information on the safety of human vaccines.

Initially, the BC proposed to develop between 50 and 100 standardized pre- and post-marketing AEFI case definitions, as well as norms for standardizing sample collection and analysis and the presentation/publication of vaccine safety data and of methods useful for both active and passive surveillance systems.<sup>65,66</sup> Studies published by this group include standardized case definitions of hypotonic hyporesponsive event, seizure, fever, and nodule at injection site.<sup>10,11,75,88</sup>

#### **STRATEGIES TO IMPROVE THE ACCURACY OF SAEFI SYSTEMS**

Certain strategies are capable of increasing the sensitivity of passive and active SAEFI systems. One of these is the distribution, following vaccination, of forms containing information on AEFIs and instructions on how to report any reactions resulting in medical treatment in the four weeks following vaccination.<sup>97</sup> Another strategy is the development of an active system based on sentinel pediatric hospitals in parallel to passive surveillance.<sup>20</sup>

<sup>b</sup> Brighton Collaboration. Immunize safely [Internet] [cited 2010 Oct 25]. Available from: <https://brightoncollaboration.org/public.html>

The use of internet-based self-reporting as a means to increase the sensitivity of SAEFI systems has been applied recently in large-scale vaccination of military personnel against smallpox.<sup>81,82</sup> Countries such as the United States, Canada, Spain, and England receive electronic reports of AEFIs.<sup>68,114,a</sup>

A similar approach is to link EIRs to hospital admission and outpatient care databases, which rely on the identification of the patient, on the national hospital admission database, and on the implementation of electronic patient files within the primary health care network, which must include vaccination registries.<sup>85</sup> In spite of all these prerequisites, this strategy has proven itself feasible even in developing countries.<sup>1</sup>

Mass vaccination campaigns are considered to be an effective measure for controlling diseases such as measles and poliomyelitis.<sup>84</sup> SAEFI systems constitute an excellent instrument for maintaining the credibility of such campaigns,<sup>112</sup> as well as an opportunity to study rare AEFIs, given that the large number of vaccines administered in a short period of time increases the sensitivity of surveillance.<sup>4,29,30,35,93</sup> However, vaccination campaigns can potentially favor an increase in the perception of the risk associated with vaccination,<sup>30</sup> and may lead to an increase in programmatic errors, given that teams that participate in such campaigns may be less experienced.<sup>36,84,112</sup>

Novel technologies, such as the use of bar-coded vaccine vials, allow for greater accuracy, easier registration of administered doses, and better identification of the vaccine batch used.<sup>55</sup>

## DATA INTERPRETATION AND LIMITATIONS

In isolation, surveillance data are not sufficient to establish a causal relationship between vaccines and AEFIs.<sup>58,77</sup> Complementary investigations in the form of observational studies are necessary to establish such relationships.

Compared to clinical trials taking place prior to vaccine registration, post-marketing studies are more vulnerable to the influence of confounders and bias, which should be taken into account when designing and analyzing such studies.<sup>43,58</sup> Investigating the existence of a causal relationship between a given AEFI and a vaccine is a complex task, requiring careful analysis of data quality and consistency as well as of the biological plausibility of the association.<sup>58</sup>

Information relevant to this type of investigation include:<sup>58</sup>

- the precise timing of immunization and of the occurrence of the adverse event;

- the existence of prior studies indicating an association between the observed event and the vaccine, and whether this association is biologically plausible;
- laboratory confirmation of the association whenever possible (e.g., isolation of the vaccine strain of the yellow fever virus from a patient with clinical symptoms compatible with post-vaccination viscerotropic disease);<sup>47</sup>
- the recurrence of the event upon re-vaccination; and
- controlled clinical trials or observational studies must indicate a greater risk of the AEFI under investigation among vaccinated individuals when compared to non-vaccinated ones.

Presence of a strong association between event and vaccine along with the rarity of spontaneous occurrences of this same event in the general non-vaccinated population constitute important evidence for determining a causal association.<sup>19,58</sup> A comparison of passive SAEFI services with epidemiological studies of vaccine safety shows that, while the latter supply better estimates of the association, they are more costly, lengthy, and are limited to the evaluation of a single adverse event.<sup>14,21,58,98</sup>

Both passive and active systems show low specificity, i.e., both will identify adverse effects coincidentally associated in time with the vaccine in the absence of causal relationship.<sup>58</sup> One example of this is the identification of alterations in neuropsychomotor development and the appearance of neurological disease in vaccination-age children.<sup>7,107</sup>

In addition to low specificity, other limitations of SAEFI services include greater complexity when compared to surveillance of diseases with well-defined clinical syndromes and difficulty in establishing case definitions;<sup>52,96</sup> simultaneous exposure to multiple vaccines and the large number of potential AEFIs associated with these vaccines;<sup>70</sup> difficulty to obtain information regarding re-exposure among individuals with AEFIs, especially in passive systems;<sup>96</sup> and bias towards preferential reporting of more severe cases, compromising the system's representativeness.<sup>56</sup>

One of the major limitations of SAEFI services, regardless of type, is the low sensitivity to detect late AEFIs, especially those emerging more than four weeks after vaccination.<sup>25,40,60,64</sup>

## DIFFERENT SAEFI EXPERIENCES

The organization of immunization programs in different countries follows the political-administrative structure of health care services in these countries. These

structures are conditioned by socioeconomic development and social, political, and cultural characteristics, as well by access to different technologies.

The vaccines included in the Brazilian National Immunization Program (PNI) schedule are mandatory and of universal and free access; in Canada, vaccination is not mandatory, and each province elaborates its own immunization program.<sup>15</sup> In Italy, certain vaccines administered during childhood are mandatory,<sup>8</sup> whereas in Germany physicians are responsible for indicating which vaccines should be given.<sup>90</sup> Such diversity of policies justifies the adoption of different types of SAEFI systems in each country.<sup>36</sup>

In the United States, SAEFI began in 1986, when AEFI notification by health professionals and vaccine manufacturers became mandatory.<sup>37,96,114</sup> Two surveillance systems were in operation, one run by the CDC and the other by the Food and Drug Administration (FDA), the regulatory agency of the United States health care system.<sup>37,96</sup> In 1990, both systems were merged into the Vaccine Adverse Event Reporting System, a nationwide passive surveillance system under the control of the CDC.<sup>114</sup> The FDA became responsible for investigating batches of vaccine associated with severe adverse events.<sup>c</sup>

In Canada, SAEFI and pharmacosurveillance were carried out by the same system until 1987, when a passive SAEFI system was created, the Vaccine Associated Adverse Event Surveillance System, run jointly by the regulatory agency and the immunization program.<sup>a</sup>

In the 1990's, Australia implemented a passive SAEFI system, the Adverse Drug Reactions Advisory Committee. Though this system had nationwide coverage, there were differences between the countries various states and territories.<sup>70</sup> Australia was one of the first countries to implement an electronic registry for childhood immunizations with the aim of increasing vaccine coverage and improving SAEFI. In the Australian system, passive SAEFI is complemented by an active system in sentinel units, which deals with severe AEFI cases.<sup>70</sup>

In the majority of European countries, SAEFI is carried out by the medical regulatory agency of the European Union (European Medicines Evaluation Agency).<sup>68</sup> This agency uses the same information flow and notification forms as the pharmacosurveillance agency, which creates problems for data analysis due to the

absence of specific information of importance for vaccine safety.<sup>68</sup>

In Western Europe, SAEFI systems are passive and heterogeneous. Many Western European countries have their own particular legislation regulating AEFI notification. Among the limitations of this model are the lack of case definitions for specific AEFIs and a substantial variation in the range of notifiable events.<sup>68,69</sup>

The first SAEFI experience in Brazil was implemented in São Paulo state in 1984.<sup>13,45,d,e</sup> In 1998, the Brazilian Ministry of Health implemented a nationwide passive SAEFI system aimed at ensuring the reliability of the immunobiologicals used by PNI.<sup>76,79,f</sup>

The case definition adopted in Brazil focuses mainly on events with more severe systemic manifestations; the source of information for this system are the primary care and hospital networks; and notifications are done using a standardized, specific form.<sup>79</sup> Since 2000, information are transmitted and stored electronically using a software developed specifically for this purpose.

In spite of its being a more recent initiative, and of the limitations inherent to passive surveillance,<sup>52,105</sup> the Brazilian SAEFI system has been successful in identifying more reactogenic vaccines and/or batches,<sup>34,92</sup> as well as less known or previously unrecognized AEFIs, as was the case with the yellow fever vaccine.<sup>102</sup>

One peculiarity of the Brazilian experience is that the SAEFI system was implemented prior to a pharmacosurveillance system rather than as one of its branches. It is connected exclusively to PNI, without explicit ties to the regulatory agency of the health care sector (ANVISA), which distinguishes it from the experiences of countries in North America or the European Union.

Initiatives aimed at improving the articulation between PNI and Anvisa when dealing with the Brazilian SAEFI system include the creation, in 2008, of the Interinstitutional Committee for Pharmacosurveillance of Vaccines and other Immunobiologicals by the Health Surveillance Secretariat (Secretaria de Vigilância em Saúde – SVS). A mechanism was established for the articulation of ANVISA, the SVS, and the Instituto Nacional de Controle de Qualidade em Saúde da Fundação Oswaldo Cruz in order to carry out the pharmacosurveillance of vaccines and other immunobiologicals within the context of the Brazilian National Health Care System (SUS) as well as in the private health care network.<sup>79</sup>

<sup>c</sup> Food and Drug Administration. Vaccine Adverse Event Report System (VAERS). [cited 2002 Oct 31]. Available from: <http://www.fda.gov/cber/vaers/what.htm>

<sup>d</sup> Brito G. Sistema de Notificação e de Investigação de Eventos Adversos Pós-Vacinação. São Paulo: Secretaria de Estado da Saúde; 1991.

<sup>e</sup> Freitas FRM. Vigilância de eventos adversos Associados à vacina DPT e preditores de gravidade: Estado de São Paulo, 1984-2001 [master's dissertation]. São Paulo: Faculdade de Saúde Pública da USP; 2005.

<sup>f</sup> Ministério da Saúde. Fundação Nacional de Saúde. Manual de vigilância epidemiológica dos eventos adversos pós-vacinação. Brasília, DF; 1998.

## FUTURE CHALLENGES

The collective international experience shows that safe vaccines are essential to the maintenance of high adherence to immunization programs. Passive surveillance is acknowledged as being the primary instrument for monitoring the safety of these vaccines.<sup>24</sup> However, active surveillance has been growing in importance, especially in two scenarios: a) when confronted with an event that can lead to a public health emergency, such as a pandemic of high-lethality influenza;<sup>39</sup> and b) when vaccines with a history of severe adverse events in the past are reintroduced after undergoing improvements in safety, such as was the case with rotavirus<sup>50,80</sup> and smallpox<sup>17</sup> vaccines. In such cases, it will be essential to develop active SAEFI systems capable of identifying AEFIs in almost real time.<sup>33</sup>

The intensification of research on the biology, immunology, and immunopathology of immunopreventable diseases, aimed at furthering our understanding of causality and of the pathogenicity of AEFIs is another challenge for the years to come.<sup>107</sup>

Equally complex will be to follow the shift in the paradigm on which vaccine development has been based. The majority of diseases for which vaccines are available are infectious acute diseases, usually severe in nature, monophasic, that confer definitive or long-lasting immunity to reinfection, and that are preventable by high titers of specific antibodies.<sup>107</sup> Vaccines based on this paradigm, in addition to being effective, are relatively simple to develop, and both these characteristics favor their success as public health interventions.

The introduction of novel technologies coming from different areas of the Basic Sciences allows for the development of immunizing agents that are distinct from the "classical" vaccines.<sup>5</sup> In addition to

prophylactic vaccines, there are now vaccines aimed at treating pre-existing infectious diseases or even auto-immune diseases.<sup>107</sup> Such vaccines are heterogeneous in terms of form, formulation, and route of administration.<sup>62</sup>

There is continuous expansion of the number of vaccines available for routine and universal use, as well as of the efforts to develop ever more complex combinations of microbial antigens. If, on one hand, such innovations are advantageous in terms of cutting costs, increasing coverage, and reducing exposure to excipients frequently claimed to be associated with AEFIs,<sup>63</sup> on the other, these innovations also increase the complexity of antigen combinations and make the causal investigation of AEFIs problematic.<sup>24</sup>

In spite of our extensive knowledge of the behavior of each antigen when administered alone, new combined vaccines may induce immune responses that are quantitatively and qualitatively different from those induced by single antigens or microorganisms.<sup>57</sup> An evaluation of the efficacy and duration of the immune response triggered by these new vaccines, as well as of their safety, implies long and careful monitoring.<sup>107</sup>

It will be essential to build multidisciplinary teams focusing on clinical, laboratory and field research in order to be able to face challenges that emerge following the introduction of novel vaccines and complex immunization schedules. It will be necessary to create well-defined legal bases and an organizational structure promoting the interaction between regulatory agencies and the health care system immunization programs. Furthermore, the surveillance of immunopreventable diseases should place special emphasis on analyzing the medium- and long-term impact of different immunization strategies, as well as of their risk-benefit profiles.

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