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REVIEW

Adverse events following immunization: real causality and myths

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ABSTRACT

Introduction: To assure the highest safety of immunization programs, detect adverse events following immunization (AEFIs), eliminate concerns, and reduce the risk of low vaccination coverage, authorities in industrialized countries have collected years of reports of suspected AEFIs and have systematically assessed their clinical importance.

Areas covered: In this paper, the methods used to assess vaccine safety and the results obtained by the analysis of reports, studies, and meta-analyses are discussed.

Expert opinion: Severe AEFIs are rare, and all evaluations of safety of vaccines recommended for both children and adults have demonstrated that the advantages of vaccines are always significantly higher than the problems that they cause, and there is no need to modify recommendations. However, the definition of AEFI is dependent on the vaccines themselves, complicating the definition of an AEFI and explaining why doubts and concerns have been raised. Presently, disease epidemiology data collected in healthy people and in subjects with underlying disease, general vaccine coverage, and the vaccination status of subjects with AEFIs are managed by many independent institutions. Only strict co-operation between these institutions will lead to the successful identification of AEFIs and to a reduction of the weight of anti-vaccine arguments.

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1. Introduction

Vaccines are widely recognized as one of the most successful and cost-effective public health interventions, significantly reducing the morbidity and mortality of a variety of infectious diseases. Millions of individuals – mainly children – are saved every year from vaccine-preventable diseases.[1-3] However, like any other medication, vaccines may cause adverse events.[4] In most cases, these adverse events are mild and limited to local reactions at the site of the injection and to the development of mild fever that resolve spontaneously in a short period of time. In rare cases, they are severe and can result in life-threatening conditions requiring hospitalization and leading, in rare and extreme cases, to death.

Severe adverse events after vaccination occur more frequently in subjects with underlying clinical conditions that are well known and are considered strong contraindications to vaccine administration. Congenital or acquired immunodeficiencies provide the best examples of this phenomenon.[5,6] However, in some cases, severe adverse events can occur in otherwise healthy children.[4] Unfortunately, some severe diseases only temporally associated with vaccine administration have been suggested to be vaccine-related and have raised public concern, resulting in a decrease in vaccination coverage and subsequent outbreaks.[7,8] To assure the highest safety of immunization programs, detect all true adverse events following immunization (AEFIs), eliminate public concern, and reduce the risk of low vaccination coverage, authorities in

most industrialized countries have been amassing reports of suspected AEFIs and systematically assessing their true clinical relevance. Moreover, several studies and meta-analyses have contributed to the identification of AEFIs that represent relevant clinical problems. In this paper, the methods used to assess vaccine safety as well as the results obtained from these reports, studies, and meta-analyses will be discussed. Papers were selected from PubMed in the literature published in English language in the last 30 years using the key words 'adverse event' and 'immunization' or 'vaccination'.

2. Systems to monitor and evaluate vaccine safety

The assessment of vaccine safety encompasses all phases of the development of individual vaccine preparations.[9] However, due to the relatively low number of subjects enrolled, randomized controlled trials carried out during pre-authorization phases provide reliable information regarding only local reactogenicity (i.e. injection site reactions) and relatively common systemic adverse events (i.e. fever). Rare adverse events are not usually identified in these trials. Moreover, because these trials are frequently of limited duration, adverse events with a delayed onset might not be detected. Finally, these trials do not assess some groups that could significantly benefit from the use of vaccines because at high risk of acquiring vaccine-preventable diseases; these individuals (i.e. the elderly, patients suffering from chronic medical conditions, premature infants, and pregnant women) are

Article Highlights

- Vaccines are widely recognized as one of the most successful and cost-effective public health interventions, significantly reducing the morbidity and mortality of a variety of infectious diseases.
- Severe adverse events after vaccination occur more frequently in subjects with underlying clinical conditions, although in some cases they can occur in otherwise healthy children.
- For several years, in most industrialized countries, official authorities have collected reports of suspected AEFIs and have systematically assessed their real clinical importance.
- Although the assessment of vaccine safety extends to all phases of the development of individual vaccine preparations, post-licensure surveillance is an essential adjunct to pre-licensure activities.
- Four categories of AEFIs are considered: the first includes those for which evidence convincingly supports a causal relationship; the second includes those for which data favor acceptance of a causal relationship; the third includes those for which evidence favors the rejection of a causal relationship; and the fourth includes those for which data are inadequate to accept or reject a causal relationship.
- Severe AEFIs are rare, and all the evaluations of the safety of immunization schedules recommended for both children and adults have found that the advantages of vaccines are always significantly higher than the problems they can cause and that there are no true problems that justify the modification of recommendations.
- All health-care workers must highlight the incredible advantages of vaccines.

This box summarizes key points contained in the article.

deliberately excluded from initial evaluations due to their increased rate of adverse events.[10] To increase information regarding vaccine safety, at least for people for whom vaccine are licensed, post-licensure surveillance is essential.[11]

The World Health Organization (WHO) since 1968 has implemented an International Drug Monitoring Programme with the main aim to collect data from the national spontaneous reporting systems on drug-related adverse events to issue international signal of drug safety concerns.[12] Presently, more than 80 countries all over the world continuously send data regarding individual case safety reports. All the data are not only collected and categorized in a relational database management system (VigiBase), but also analyzed to evaluate its characteristics and its documentation. Moreover, quarterly summary reports are reviewed by clinical experts and their findings are disseminated to the participating national centers.

In the USA and Europe, post-licensure surveillance for AEFIs is mandatory. In the USA, spontaneous reports of AEFIs are mainly collected by the Vaccine Adverse Event Reporting System (VAERS).[13] VAERS amasses reports from all parties involved in vaccine production and use, including vaccine recipients. In Europe, reports of AEFIs, as with any other pharmaceutical product that is centrally authorized, are managed through the EudraVigilance system.[14] This authority also collects the results of studies carried out by vaccine producers and/or independent researchers, together with spontaneous reports provided by vaccine recipients and physicians. Spontaneous reporting has the advantage of covering a large population, rapidly identifying potential new safety concerns, and reducing costs. Moreover, by providing accumulating evidence of safety, it can help to maintain the public confidence needed to keep vaccination levels high enough to prevent disease outbreaks. However, it presents several limitations that can significantly reduce its utility if reports are not

adequately collected and causality not precisely assessed. Underreporting and reduced completeness in reports are among the most important limitations.[11,15] To improve reporting completeness and accuracy, the use of web-based technological advances has been suggested.[11] Moreover, reports are often not accompanied by an accurate analysis of the prevalence of the same clinical problem in the unvaccinated population, and it is not possible to determine whether the risk is actually vaccine related or is only temporarily linked to vaccine administration. To address these issues, accurate causality assessment is mandatory and other systems are necessary.

In the USA, a database infrastructure named the Vaccine Safety Datalink (VSD) was founded in 1990 by the Centers for Disease Control and Prevention (CDC) to evaluate vaccine safety and test the hypotheses generated by VAERS with data describing vaccinated children who did not experience an adverse event.[16] The population included is large enough to permit the assessment of very rare AEFI and to exclude the possibility that clinical problems are only temporarily related to vaccine administration. Information regarding a total of approximately 9 million individuals (2 million children and 7 million adults) who have received millions of vaccine doses is collected yearly.[17] Similar to the VSD, a second authority called the Post-Licensure Rapid Immunization Safety Monitoring was established by the Food and Drug Administration (FDA) to analyze data obtained from several large health insurance companies covering an even larger number of people, thus expanding the evaluation of AEFIs. In Europe, the European Medicine Agency (EMA) monitors vaccine safety within its member states and periodically performs an assessment of spontaneous AEFI reports to detect any potential sign of vaccine-related adverse events.[18] Moreover, the Vaccine Adverse Event Surveillance & Communication consortium, a collaborative network of agencies initiated and sponsored by the European Center for Disease Prevention and Control, has developed standards and methods for vaccine safety assessment that have been used on several occasions to conduct epidemiological studies based on a large amount of data collected in many European countries.[19]

In addition to traditional methodologies, such as cohort and case-control studies, self-controlled observational study designs such as the case-crossover design and the self-controlled case series can be used to assess causality.[20] These methods, which only utilize information from individuals with an adverse event and do not require external controls, combine the power and simplicity of cohort design and the economy of the case-control method while eliminating confounding independent variables.[21] They are particularly important for the assessment of rare and/or acute onset AEFIs and in cases wherein indication bias is possible. In contrast, they may be difficult to apply in conditions exhibiting insidious onset. However, both the traditional and more recently developed methods consider the weight of the evidence and permit a conclusion regarding the casual relationship between each vaccine and an adverse health problem. In general, four categories of causation are considered. The first includes those AEFIs for which evidence convincingly supports a causal relationship; the second includes those for which data favor the acceptance of a

causal relationship; the third includes those for which evidence favors the rejection of a causal relationship; and finally, the fourth includes those for which the data are inadequate to accept or reject a causal relationship and for which further evaluations are needed.[4]

3. Outcomes for which evidence convincingly supports causality

Among those AEFIs for which evidence convincingly supports a causal relationship, the most relevant from a clinical point of view is anaphylaxis. Several vaccines have been found to be associated with this condition, but causality is considered to be convincingly established for measles, mumps, rubella (MMR), varicella (V) (MMRV), influenza, hepatitis B, tetanus, yellow fever, human papillomavirus (HPV), and meningococcal vaccines.[22] However, anaphylaxis is a very rare phenomenon. McNeil et al. determined the rates of vaccine-related anaphylaxis in children and adults from January 2009 through December 2011 in the USA.[22] Of 25,173,965 vaccine doses, 33 confirmed cases out were identified. The rate of anaphylaxis was 1.31 (95% confidence interval [CI] 0.90–1.84) per million vaccine doses, without any significant difference according to age. However, because millions of vaccine doses are administered yearly, the number of anaphylactic responses to vaccination occurring every year worldwide is not marginal. To address this risk, health authorities recommend that vaccines are given in a facility with appropriate equipment and personnel trained to recognize and treat anaphylaxis after an accurate collection of medical history.[23]

In the past, it was thought that egg allergy could play a major role in anaphylaxis. However, several studies have clearly demonstrated that the role of egg proteins in triggering anaphylaxis is marginal. Among the vaccines presenting a risk (i.e. yellow fever, influenza, MMR, MMRV, and rabies), only the yellow fever vaccine contains an amount of egg protein high enough to cause problems in sensitized subjects.[24] The MMR vaccine is safe when administered to children with an egg allergy,[25] as is the MMRV vaccine. Finally, contrary to previous assumptions, the influenza vaccine can be administered without any precaution to children able to eat lightly cooked eggs without clinical signs and symptoms of allergy.[5,26] Those exhibiting hives or severe systemic problems (i.e. angioedema, respiratory distress, lightheadedness, recurrent emesis, or the need for epinephrine or another emergency medical intervention) after egg ingestion are vaccinated under close supervision in an appropriate setting. Alternatively, they can receive, when available, the recombinant influenza vaccine or the cell-culture-based inactivated influenza vaccine.[27–29]

Anaphylaxis can occur also after the administration of vaccines containing gelatin and yeast. Gelatin is used as a stabilizer in several vaccines, including influenza, MMR, MMRV, rabies, Japanese encephalitis, and typhoid vaccines. Children with a history of anaphylaxis in response to this component must be vaccinated with extreme caution.[9,26] The same is true for subjects with a documented allergy to baker's yeast when receiving vaccines that include antigens cultured in

recombinant *Saccharomyces cerevisiae* (baker's yeast), such as the hepatitis B and quadrivalent HPV vaccines.[27]

Finally, several vaccines contain latex in vials or syringes. The list of these vaccines is available at the CDC website.[28] Children with a history of anaphylaxis in response to latex (but not those with minor reactions) should not receive these vaccines unless the benefit of vaccination outweighs the risk.

The varicella vaccine has been associated with disseminated dermal varicella infection without any other organ involvement in healthy subjects and with disseminated infection resulting in pneumonia, meningitis, and hepatitis in individuals with immunodeficiency.[4] In both cases, clinical signs and symptoms of disease appear 7–21 days after administration, suggesting a strict relationship between the virus and the AEFI. However, the prevalence of these clinical problems differs. Dermal dissemination is common and has been diagnosed in several thousands of healthy children.[29,30] Fortunately, it is a mild disease that resolves without complication. In contrast, infection with the involvement of multiple organs is rare and has been described in very few cases, almost always in patients with either a genetic or an acquired immunodeficiency.[31–33] Although in most of these cases only temporality suggests causality, the presence of the vaccine-strain varicella virus in the vesicular fluid and infected organs of some patients indicates the strict relationship between vaccination and the development of the disease. Finally, varicella vaccine has been convincingly associated with the development of herpes zoster (HZ) alone or in association with meningitis or encephalitis. Chaves et al. identified 981 reports of HZ development after varicella vaccination based on VAERS data submitted from May 1995 through December 2005.[29] However, the vaccine-strain virus was identified in the lesions in a minority of cases. Moreover, in some patients, wild-type varicella virus was found, suggesting that this adverse event following varicella vaccination was less frequent than commonly thought. HZ, in combination with central nervous system diseases such as meningitis or encephalitis, has been described in little more than 10 cases.[29] However, causality was supported by the fact that in the majority of these patients, the vaccine-strain virus was present in the cerebrospinal fluid.[29]

MMR vaccine has been associated with a number of well-identified AEFIs. Inclusion body encephalitis has very rarely been attributed to the vaccine on the basis of three reports of immunocompromised individuals with signs and symptoms of severe neurological disease, as well as specific histologic and laboratory findings.[34–36] Intracytoplasmic and intranuclear inclusions in nervous cells with paramyxovirus nucleocapsids were revealed by electron microscopy.[36] Moreover, in one case, polymerase chain reaction analysis of the viral material isolated from biopsied brain tissue was identical to the measles vaccine strain included in the given vaccine.[34]

In contrast, MMR and MMRV-related febrile seizures (FS) are quite common. They are ascribed to the measles component of the vaccines and occur in children 1–2 years of age, particularly in those who have experienced previous FS, during the second week following the first vaccination.[37–39] The second dose is not a risk. The first dose of the MMR vaccine has been shown to increase the number of FS cases

in the second year of life by 25.0 to 34.2 per 100,000 children.[40] Moreover, children experiencing their first FS after MMR vaccination were equally prone to recurrent seizures compared to children who suffered from FS, but did not receive MMR vaccine previously. None of the patients exhibited neurological sequelae.[41] However, the potential risk of developing FS after the first MMR vaccination is not considered sufficient to dismiss the use of the MMR vaccine, which is recommended for children worldwide, although parents are informed to remain vigilant after vaccination.[42] The combination of MMR and varicella vaccines in a single injection increases the risk of FS. Jacobsen et al. reported that among 31,298 children between the ages of 12–60 months who received either the MMRV or MMR + V vaccination for the first time, 22 (0.70/1000) and 10 (0.32/1000) cases (relative risk [RR] 2.20; 95% CI 1.04–4.65), respectively, exhibited FS 5–12 days following vaccination.[43] In contrast, no risk of FS was evident after the second MMRV dose. Similar results were obtained by Klein et al., comparing 83,107 children vaccinated with the MMRV vaccine and 376,354 vaccinated with the MMR + V vaccine. This study found that those receiving the MMRV vaccine had an excess risk of FS of 0.43 per 10,000 doses (95% CI 2.6–5.6).[44] This explains why health authorities have stated that the first immunization in children 1–2 years old is obtained with MMR and varicella vaccines given separately unless the parent or caregiver expresses a preference for MMRV vaccine. For the first dose of MMRV vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. For the second dose of MMR and varicella vaccines at any age and for the first dose at age ≥ 48 months, the use of MMRV vaccine is generally preferred over separate injections of its equivalent component vaccines (i.e. MMR vaccine and varicella vaccine).[45]

In addition, a number of reports have demonstrated that all live, attenuated viruses in the MMR vaccine can cause immune thrombocytopenic purpura (ITP), whether administered alone or in combination.[46–51] This is due to a specific immunological mechanism, as evidenced by the detection of anti-measles and anti-rubella virus IgG antibodies in platelets from subjects with the disease in the acute phase, with their successive disappearance when the disease was cured.[52] A recently published systematic review of 12 studies has found that the likelihood of developing ITP after MMR vaccination is approximately 2.6/100,000 vaccine doses (range, 0.087–4), a value significantly lower than that evidenced after natural infection with measles or rubella. However, the clinical outcome after vaccination is less severe than ITP observed after natural disease.[50] Serious bleeding requiring hospitalization and/or transfusion occurs in exceptional cases,[51] although gastrointestinal hemorrhage,[53] hematuria,[54] pulmonary hemorrhage,[53] and a need for splenectomy [55] have been described in isolated cases. The first dose of the MMR vaccine does not generally reactivate previous acute ITP. Moreover, booster doses are not followed by recurrences within 6 weeks of administration. In conclusion, there are no reasons to limit MMR vaccine use. In children with chronic ITP, however, a cautious approach is required; in these patients, the risk–benefit ratio of MMR vaccine should be weighed against the risk of measles in the community at the time.[53]

Yellow fever vaccine has been demonstrated as a possible cause of two serious adverse events including YF-vaccine-associated neurologic disease (YEL-AND) and YF-vaccine-associated viscerotropic disease (YEL-AVD).[56] Both YEL-AND and YEL-AVD occur only after primary vaccination and have been described mainly in travelers. YEL-AND has a median onset of 13–15 days while YEL-AVD has an incubation period of 2–7 days.[57] In both cases, causality is evidenced by the detection of the vaccine virus in the organ involved in each disease. YEL-AVD is similar to wild-type yellow fever, in which the vaccine virus proliferates in multiple organs, causing multiple organ dysfunction syndrome or multiorgan failure and death in at least 60% of the cases. Since 2001, when the diseases were first described, more than 60 cases have been reported worldwide. Using a passive surveillance system in the United States, the incidence of YEL-AVD was reported as 0.3–0.4 cases per 100,000. However, other estimates range from 0 to 12 per 100,000.[58] The elderly people with autoimmune diseases and thymectomized individuals are considered at higher risk. Meningoencephalitis is the most common presentation of YEL-AND and is due to a direct infection of the central nervous system by the vaccine virus.[59] Other manifestations of YEL-AND include Guillain-Barré syndrome and acute disseminated encephalomyelitis. The latter two manifestations are believed to be autoimmune mediated, in which antibodies produced in response to the vaccine cause either peripheral or central demyelination. It has been calculated that incidence of YEL-AND could vary from less than 0.4 up to 2.66 cases per 100,000 vaccine doses.[60,61]

Finally, for all the injectable vaccines independent of the antigen involved, convincing evidence of a causal relationship between the administration of a vaccine and the development of syncope (i.e. fainting) [62,63] and deltoid bursitis (i.e. frozen shoulder) [59] has been demonstrated. Syncope is a relatively common condition that can occur after any medical procedure involving a needle stick (i.e. blood draw). Its prevalence varies significantly according to the characteristics of the vaccinated subjects and is more common among adolescents.[62] Because it occurs almost immediately after the injection, the Advisory Committee on Immunization Practices suggests a 15-min observation period after vaccination.[63] Shoulder lesions are considered the consequence of the administration of the vaccine in the deltoid muscle, are more common in adults, and resolve without sequelae in a short time, particularly when treated with a steroid. They are relatively rare, as evidenced by Atanasoff et al., who reported that from 2006 through 2010, only 13 claims of lesion were submitted to the Vaccine Injury Compensation Program in the USA.[64]

4. Outcomes for which evidence favors the acceptance of a causal relationship

According to statements of the Institute of Medicine (IOM),[4] some problems regarding the MMR vaccine and trivalent influenza vaccine (TIV) are classified as likely to be causal. Moreover, a possible relationship between rotavirus vaccines and intussusception has recently been postulated. However, none of these associations were considered important enough to modify official immunization schedules.

For the MMR vaccine, there is strong and suggestive but not firm evidence of a strict causal relationship between vaccine administration and the development of transient but not chronic arthralgia after vaccination. The disease that has been described in several studies is considered to be possibly associated with rubella virus, based on knowledge regarding its natural infection.[41,65–67] However, further studies are considered necessary to establish the true relationship between the two events.

IOM found no evidence that convincingly supported a causal relationship between any influenza vaccine and adverse events.[4] However, an influenza vaccine used in Canada in recent years has been associated with the development of a mild and temporary oculorespiratory syndrome that includes bilateral red eyes, facial edema, and respiratory symptoms beginning within 24 h of influenza immunization.[68] It has been suggested to monitor for influenza vaccine-related adverse events to further study and assess whether these problems emerge with preparations marketed by other manufacturers.[4] Moreover, the traditional TIV has been associated with the development of FS, particularly when it was given concomitantly with the 13-valent pneumococcal conjugate vaccine (PCV13). The magnitude of the incidence rate ratio (IRR) and risk difference comparing the risk of seizures in the 0–1 days versus 14–20 days following TIV differed according to the concomitant receipt of PCV13. Among children 6–59 months of age, the IRR of TIV adjusted for concomitant PCV13 was 2.4 (95% CI 1.2–4.7), whereas the IRR for PCV13 adjusted for concomitant TIV was 2.5 (95% CI 1.3–4.7). The IRR for concomitant TIV and PCV13 was 5.9 (95% CI 3.1–11.3). Risk difference estimates varied by age due to the varying baseline risk for seizures in young children. The highest estimates were calculated for children 16 months old (12.5/100,000 doses for TIV alone, 13.7/100,000 doses for PCV13 alone, and 44.9/100,000 doses for TIV given concomitantly to PCV13). The lowest estimates occurred at 59 months (1.1/100,000 doses for TIV alone, 1.2/100,000 doses for PCV13 alone, and 4.0/100,000 doses for concomitant TIV and PCV13). The incidence rate ratio and risk difference estimates were lower for children receiving TIV without concomitant PCV13 or those receiving PCV13 without concomitant TIV.[64] Moreover, the increased risk of narcolepsy after vaccination with AS03 adjuvanted pandemic A/H1N1 2009 vaccine indicated a causal association.[68,69] The incidence of narcolepsy was 5.7 (95% CI 3.4–8.9) per 100,000 children/adolescents vaccinated with Pandemrix and 0.4 (95% CI 0.1–1.0) per 100,000 unvaccinated children/adolescents (RR: 13.9; absolute attributable risk: 5.3 cases per 100,000 vaccinated children/adolescents).

Regarding rotavirus vaccines, the relationship between this vaccine and intussusception was already known since the end of the last century when the first licensed vaccine was withdrawn from the market.[70,71] Subsequent rotavirus vaccines were initially considered safe. However, data coming from Australia and the USA after some years of use have evidenced that even these new vaccines could be associated with a significant increased risk of intussusception after the administration of the first and second dose of both vaccines.[72] In Australia, the average vaccine-attributable risk for intussusception, based on the estimated relative incidence in the 1–21

days after dose 1 and the 1–7 days after dose 2, was estimated to be 5.6 additional cases per 100,000 vaccinated infants. In the USA, the incidence of intussusception was lower, approximately the half of that evidenced in Australia.[72] Definitive confirmation of the association of intussusception with rotavirus vaccine administration was also given by the analysis of the data collected in two case-control studies carried out in Mexico and Brazil in which it was estimated that vaccination could cause 1–3 additional cases of intussusception per 100,000 people per year.[70,71] Differences in incidence of intussusception observed in the various countries might reflect sampling uncertainty in all available estimates and limitations of the surveillance systems leading to some uncontrolled biases (e.g. differences in diagnostic tests and case definitions in different settings).

A possible association between influenza vaccine administration and development of Guillain-Barré syndrome has been a matter of particular concern since at least 40 years. To investigate the strength of this association, Martin Arias et al. conducted a meta-analysis of the studies regarding influenza vaccine use performed between 1981 and 2014 and found that the administration of any vaccine was associated with an overall RR of Guillain-Barré syndrome of 1.41 (95% CI 1.20–1.66).[73] The risk was slightly higher for pandemic preparations (RR 1.84; 95% CI 1.36–2.50) than for seasonal preparations. In this case, the risk was reduced (RR 1.21; 95% CI 1.01–1.48). However, data collected in different geographic areas seem to suggest that the risk of this immune mediated adverse event depends on specific characteristics of the host. In this regard, some genetic polymorphisms have been associated with susceptibility to develop Guillain-Barré syndrome [74] and a different distribution of these polymorphisms might account for the finding.

5. Outcomes for which evidence favors the rejection of a causal relationship

There are a number of clinical conditions for which the analysis of available data has rejected a causal relationship between the disease and the administration of the vaccine. As reported by IOM,[4] no relationship exists between autism and MMR or mercury-containing vaccines such as the diphtheria, tetanus, acellular pertussis (DTaP) vaccine. Moreover, no association was found between type 1 diabetes and the MMR or DTaP vaccines and, finally, between Bell's palsy or the exacerbation of asthma and TIV. Recently, no relationship has been found between the HPV vaccine and the development of a series of clinical problems, including complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). These problems, which have raised concerns resulting in a significant reduction of vaccine coverage, will be discussed in detail below.

5.1. Autism and MMR

This supposed adverse event has had the greatest importance in conditioning the attitudes of parents and health-care workers toward vaccination. The MMR vaccine and thimerosal-containing vaccines, such as DTaP or DT, received the highest

attention for the possibility that they could cause autism and autism spectrum disorders (ASD).

The putative association between MMR and autism was first reported in 1998 in a paper published in *The Lancet*.^[75] The study had significant flaws and did not offer strong proof of a casual association. Moreover, there were ethical concerns based on its funding. Primarily for the latter reason, *The Lancet* retracted this paper in 2010.^[76] Unfortunately, in the period before retraction, the study received substantial media attention that led to increased distrust in the trade-off between the benefits of vaccines and the potential risks, resulting in an opportunity for disease resurgence. MMR coverage was significantly reduced worldwide, and a great number of measles outbreaks were reported.^[77] To evaluate the problem and to eliminate the hesitance to vaccinate against MMR, a great number of studies were conducted specifically to evaluate the possible association between MMR and autism, and ASDs were carried out.^[78–87] The MMR–autism hypothesis was never confirmed, and the safety of MMR vaccine has been reported in statements by official institutions since 2000. In 2002, the Global Advisory Committee on Vaccine Safety of the WHO stated that after an evaluation of the studies carried out, no evidence existed of a causal association between the MMR vaccine and autism or ASD.^[88] In 2012, the IOM evaluated 22 studies to assess the link between the vaccine and autism. Among these, four exhibited exceptionally high validity and precision. Thus, it was concluded that the evidence favored the rejection of any hypothesis linking the MMR vaccine with neurological disorders.^[4] A more recent evaluation of the available studies has confirmed the lack of an association.^[89] A meta-analysis of cohort and case-control studies showed that the risk of developing autism was nonexistent (odds ratio, OR 0.84, 95% CI 0.70–1.01, $p = 0.55$; OR 0.69, 95% CI 0.53–0.90, $p < 0.001$, respectively).

5.2. Autism and thimerosal

The claim of a link between thimerosal and autism or ASD was based on an FDA report published in 1999.^[90] It was noted that infants immunized according to the recommended schedule in the USA were exposed during the first 6 months of life to amounts of ethylmercury, a thimerosal metabolite, that were significantly higher than the limits approved by the Environmental Protection Agency for the exposure to methylmercury, a compound toxic to the nervous system. The equivalence of the two compounds was considered highly debatable by many experts because ethylmercury has a different distribution, metabolism, and excretion and is eliminated more quickly than methylmercury. It was reported that after a routine immunization schedule, the blood levels of mercury did not exceed the safety guidelines for methylmercury for any infant ^[91] and might be associated with neurological problems only in cases of accidental poisoning from external sources.^[92] Nevertheless, as a precautionary measure, USA health authorities suggested that this compound should be removed from all childhood vaccines.^[93] This recommendation raised general concerns among the public, and the compound was progressively eliminated from all vaccines. Today, only some multidose influenza vaccines contain thimerosal.

Support of the hypothesis for a negative effect of thimerosal was provided by a study published in 2004. Verstraeten et al. searched a large database for conditions linked to immunization history in young children and demonstrated a mild relationship between exposure to thimerosal and neurologic problems, including unspecified developmental delay, tics, attention-deficit disorder, and language and speech delays.^[94] However, no other epidemiological and clinical evaluation of thimerosal use and its effects evidenced any negative impact of the compound. Two methods were used to examine thimerosal safety in vaccines. In some cases, its safety was evaluated in very large groups of children to determine whether the use of thimerosal over a long duration was associated with the prevalence of autism. With a progressive reduction in the number of vaccines containing thimerosal, it was easy to demonstrate that the decline in the exposure to mercury was associated with the persistence of or an increase in the number of autism or acquired immunodeficiency syndrome cases diagnosed in the pediatric population.^[95,96] In other studies, smaller, defined groups of children diagnosed with autism were compared with children without neurological problems, with a detailed analysis of the characteristics of the received vaccines and factors that might have conditioned neurological development. Researchers consistently found that children who received thimerosal in vaccines were not more likely to have autism than those who did not. Examples of these studies are those by Heron and Golding ^[97] and Price et al.^[98] In the United Kingdom, Heron and Golding used population data from a longitudinal study of the health and development of >14,000 children to calculate not only whether thimerosal was associated with autism or ASD but whether the dose (i.e. the number of vaccine doses received) might play a role in this regard.^[97] No association was found, regardless of the thimerosal dose received. Similarly, Price et al. performed a case-control study of 256 children with ASD and 752 controls using conditional logistic regression to assess associations between autism, ASD, and ASD with regression and exposure to ethylmercury during the following periods: prenatal, birth to 1 month, birth to 7 months, and birth to 20 months.^[98] Exposure to thimerosal in vaccine preparations was determined based on electronic immunization registries, medical charts, and parent interviews. Information regarding potential confounding factors was obtained from interviews and medical charts. There were no findings of an increased risk for any of the three outcomes. The adjusted OR (95% CIs) for ASD associated with a 2-SD increase in ethylmercury exposure were 1.12 (0.83–1.51) for prenatal exposure, 0.88 (0.62–1.26) for exposure from birth to 1 month, 0.60 (0.36–0.99) for exposure from birth to 7 months, and 0.60 (0.32–0.97) for exposure from birth to 20 months. Finally, Thompson et al. enrolled 1047 children 7–10 years of age and administered standardized tests assessing 42 neuropsychological outcomes – but not ASD – with the aim of evaluating the association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period (birth to 28 days), and the first 7 months of life.^[99] Only a few significant associations were detected, almost equally divided between positive and negative effects. Higher prenatal mercury exposure was associated

with better performance on one measure of language and poorer performance on one measure of attention and executive functioning. Increasing levels of mercury exposure from birth to 7 months were associated with better performance on one measure of fine motor coordination and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination.

These findings led several official institutions, including WHO,[100] FDA,[101] and EMA,[102] to conclude that a causal relationship between thimerosal contained in vaccines and ill effects could be excluded.

5.3. Type 1 diabetes and vaccines

Over the last 50 years, an increased incidence of type 1 diabetes has been reported.[103] Because it paralleled the increase in vaccination coverage worldwide, it was hypothesized that development of type 1 diabetes could be related to vaccine administration.[104] Several studies have investigated this problem. A recent meta-analysis of 11 studies, including data from between 359 and 11,828 childhood diabetes cases, did not find evidence to suggest an association between any of the childhood vaccinations and type 1 diabetes mellitus.[105] The pooled ORs ranged from 0.58 (95% CI 0.24–1.40) for the MMR vaccine in five studies up to 1.04 (95% CI 0.94–1.14) for the *Haemophilus influenzae* type b vaccine in 11 studies. The results did not change when only study reports with high-methodology quality scores were pooled or when all data were adjusted for potential confounding factors.

5.4. TIV and asthma exacerbation or reactive airway disease episodes in children and adults

The IOM examined high-quality studies published until 2010 and did not find any clinically or statistically significant increase in asthma exacerbation episodes after TIV administration, regardless of whether the episodes were measured by objective pulmonary function tests, prescription drug use, clinic visits, hospitalizations, absence from school or work, or subjective symptom diaries.[4]

5.5. Inactivated influenza vaccine and Bell's palsy

One retrospective cohort study and one self-controlled case-series study considered to be of high quality by the IOM were conducted to evaluate the incidence of Bell's palsy following vaccination.[4] In a study by Stowe et al., the RR of Bell's palsy within 1–91 days of influenza vaccination was 0.92 (95% CI 0.78–1.08).[106] In a study by Greene et al., the RR of Bell's palsy in children within 1–42 days of influenza vaccination was found to be 0.67 for 2005–2006, 1.81 for 2006–2007, and 1.27 for 2007–2008 influenza seasons.[107] In adults, within 1–42 days of influenza vaccination, the RR was 1.06 for 2005–2006, 1.07 for 2006–2007, and 0.99 for 2007–2008 influenza seasons. Based on these results, it was concluded that the evidence reached a high level of confidence for a null association.[107]

5.6. Several adverse events reported after HPV vaccination

Despite their demonstrated immunogenicity with long-term durability for protection against primary infection by the targeted types of HPV and a moderate degree of cross-protection against nontargeted types, all HPV vaccines on the market are significantly underused [11308] due to concerns about their safety. In the United States, only 33.4% of female adolescents aged 13–16 and 6.8% of males had received the three recommended HPV vaccine doses in 2012.[108] In Europe, HPV vaccination coverage varies in the various countries, but it remains generally lower than desired and no higher than 75%.[109] Doubts about the usefulness of these vaccines and the risk of serious AEFIs, particularly autoimmune diseases, have been raised by several groups.[110] However, all studies that have evaluated the safety of HPV vaccines have shown that they are safe and that the incidence of severe AEFI in vaccinated subjects is low and equivalent to that found for placebo/unimmunized controls.[111–119] In a study including almost 300,000 girls who had received nearly 700,000 doses of the quadrivalent HPV vaccine, no increased number of autoimmune diseases, neurological problems, or venous thromboembolic adverse events in vaccinated girls were detected compared with controls.[111] Similar data were reported in a pooled analysis of several clinical trials involving 11,778 females or males who had received the quadrivalent HPV vaccine as well as 9686 controls. Among these study participants, 0.2% of both vaccine and placebo recipients had to discontinue administration due to adverse events and that these adverse events were serious in only 0.1% of each group. Moreover, autoimmune reactions were noted in 2.4% of subjects in both then vaccine and placebo groups.[112–115] Based on these studies and several other studies supporting the safety of HPV vaccines,[116–119] the WHO Global Advisory Committee for Vaccine Safety,[120] the CDC,[121] and the EMA [122] officially reported that all licensed HPV vaccines could be used without any relevant risks. The most recent statement of the EMA regarding two syndromes, CRPS and POTS, in young women, states that the disorders have been erroneously ascribed in recent years to HPV vaccines.[122] The document highlights the findings that in the general population approximately 150 girls per million may develop CRPS each year and that a similar number can suffer from POTS in the same period of time. The prevalence of these clinical conditions was the same among subjects receiving the HPV vaccine, supporting the safety of these prophylactic preparations and the continued use of HPV vaccines.

6. Conclusions

Around the world, different pediatric immunization schedules are used. Differences primarily involve the number of recommended doses for primary immunization, the time of their administration, and the need for booster doses rather than which type of the vaccine to use. However, upon reviewing stakeholder concerns and scientific literature derived from the evaluation of data collected under post-marketing surveillance, it is clear that all these schedules are safe. Little

evidence of severe, irreversible adverse events strictly linked to vaccine administration has been revealed. Attention must be paid to allergic subjects at risk for anaphylaxis and to immunocompromised subjects, particularly when live attenuated vaccines are administered.

Existing mechanisms to gear at assessing the safety of vaccines are highly effective and assure that even new adverse events are detected early. A great number of supposed associations between AEFI and vaccines have been excluded. However, strong surveillance must be maintained not only for new vaccines but also for those that have been used for a long time. New adverse events for which causality must be determined are continuously reported.[7] The example of TIV, for which a possible association with FS, particularly when concomitantly administered with PCV13, has recently been documented,[69] is proof of this point. This and other AEFIs have been reported, and evaluations are urgently needed for all additional investigations.

7. Expert opinion

Severe AEFIs are rare and all evaluations of the safety of the immunization schedules recommend that in both children and adults, the advantages of vaccines are significantly higher than the problems they can cause and that there are no problems that warrant the modification of current recommendations. However, the causative link between AEFIs and vaccines themselves is difficult to establish, explaining why doubts and concerns arise and are maintained for long periods of time. The association between autism and MMR or thimerosal-containing vaccines is the best example in this regard. The paper falsely claiming a link between vaccines and autism dates back to 1999.[71] The collection of a number of data scientifically adequate to disprove the association between the vaccine and the disease has taken many years.[80–82, 84–91] During this time, those who opposed the use of MMR or any other vaccine potentially related to the development of neurological problems continued to spread erroneous information and increase the number of parents with negative attitudes toward immunization. It should not be forgotten that the most rigorous studies used to affirm vaccine safety have limitations that are used by opponents to affirm their opinion. Trials occasionally exclude subjects that are more susceptible to AEFIs. Moreover, in meta-analyses, data from studies that include subjects with different demographic characteristics and different denominators are pooled together. No consideration is made regarding age, sex, or the number of vaccine doses administered when enrolling subjects. Moreover, when a vaccine is studied, the differences that can exist among vaccines produced by different manufacturers are often not taken into account. The case of an influenza vaccine produced by a Canadian manufacturer that resulted in an AEFI not observed with other influenza vaccines is a good example of this phenomenon. However, in most cases, these problems have limited value due to the low numbers and all health-care workers, particularly pediatricians, must explain that these limitations are largely overcome by the incredible advantages of vaccines. Unfortunately, not all health-care workers are convinced of the importance of immunization, thereby further

limiting vaccination coverage and significantly reducing the protection of the people whom they take care.

In the coming years, the ability to optimally monitor vaccine safety will be significantly accelerated by the diffusion of electronic health records and the ability to link records across health data systems and immunization registries as presently occur only in some countries. This monitoring will permit not only the expansion of the population that is included in post-marketing surveillance but also the identification over a shorter period of time signals that could suggest a link between vaccines and rare but clinically relevant AEFIs. Moreover, it is reasonable to presume that significant advantages in the evaluation of AEFIs will be achieved through strong partnerships among regulatory and public health authorities, independent researchers, and vaccine producers. Presently, disease epidemiology data in healthy people and in subjects with underlying diseases and disease burdens regarding vaccine coverage and the vaccination status of subjects with AEFIs are collected and managed by different institutions that function independently. Even VigiBase, that is a WHO management system, receive data from about 80 countries only.[123] This reduces the possibility of rapid identification of the true association between an AEFI and a particular disease. Only strict cooperation between different institutions will lead to success and to the reduction of the weight of opponent arguments.

Declaration of interest

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