

## Vaccination Age Changing from Infancy and Childhood to Adolescence and Adulthood: An In-Dispensable Approach in Immunization Programs

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### Abstract

**Objectives:** Despite the positive effects of vaccines on control of many infectious diseases, they are not completely safe. The purpose of this article is to draw attention to the problems associated with newborns and infants immunization.

**Data Collection Method:** For each subject, a review of electronic sources was carried out in the PubMed and Google Scholar using appropriate key words.

**Results:** For different reasons including: the differences between the immune systems of newborns/children and adults, sever adverse events and inefficacy of vaccines, deceptive advertising and inadequate parental awareness about vaccines and vaccination; newborns and children are at risk and accordingly a decline in public confidence is observed.

**Conclusion:** The revision of vaccination age changing (at least for some vaccines) in order to maintain newborns/children's health and to prevent the return of infectious diseases is required. To achieve this goal, new retrospective and prospective studies to reassess the safety, efficacy, quality and protection duration of vaccines, proper implementation of good clinical practice, establishment of a network vaccine safety database by collaboration of international organizations, vaccine manufacturers and academic centers for sharing of information and enhancement of awareness of healthcare professionals and people about immunization at global level are needed.

**Keywords:** Vaccination age; Immunization; Public confidence; AEFI; HBV

### Introduction

The aim of vaccination is protection of population against preventable infectious disease. Despite vaccines have contributed in reducing the impact of many infectious diseases, they are not completely safe and can cause adverse effects. While common side effects of vaccines are mild, some vaccines have been associated with serious or even deadly side effects [1]. On the other hand, public confidence in vaccines is waning [2-4]. For these reasons, vaccine pharmacovigilance is the centre of attention and is of particular importance to promote both public confidence in vaccines and acceptance of immunization programs.

Pharmacovigilance is the science and data gathering activities relating to the detection, assessment and understanding of adverse events and its ultimate goals are: prevention of adverse drug reactions, rational use of pharmaceutical products, enhancement of patient care and patient safety and risk minimization by education of healthcare professionals or patients [5-7]. The importance of vaccines pharmacovigilance is related to the vaccines characteristics including: 1) they are biological products (variation in manufacturing process); 2) mandated by governments through national immunization programs; 3) Heat, light and freezing sensitive (need cold chain); 4) administered to healthy individuals and given for prevention; 5) highly expensive

with limited shelf life; 6) given once or only a few times; and 7) inducing body immune system for protection [8-11]. The purpose of this article is to draw attention to the problems associated with newborns and infants immunization and based on recent researches in the field of vaccines and vaccination, hypothesizes the necessity of revision of the vaccination age changing.

### Data Collection Method

For each subject, a review of electronic sources was carried out in the PubMed and Google Scholar using appropriate key words.

### Results and Discussion

#### The differences between the immune systems of newborns/ children and adults

Infants and children are not just small adults. During the first few months of life, neonates exhibit a physiological immunodeficiency, are dependent on maternal antibodies and do not respond to vaccines which need antibody production for protection. Production of antibodies occurs at 3-6 months of age and adult levels of immunoglobulin M (IgM) and immunoglobulin G (IgG) are reached by 4-5 years and 7-8 years, respectively [12]. Newborns are unable to induce a thymus independent response and make adequate antibodies; and accordingly do not respond to bacteria with polysaccharide antigens (for example, *Streptococcus pneumoniae*, *Neisseria*

*meningitidis, Haemophilus influenza*). The ability to respond to polysaccharide antigens is developed by 18-24 months of age [13,14].

In neonates, the immune response appears to shift from the Th1 to the Th2 profile [12,15]. Also, a decrease in interferon (IFN) production by lymphocytes (and correspondingly hyporesponsiveness of macrophages) and a reduction of Th1 cytokines production such as interleukin 1 (IL-1) and IL-12 by mononuclear phagocytes are observed. Progesterone and IL-10 which are produced by the placenta, down-regulate Th1 response in order to prevent fetus rejection. In addition, signaling of Toll-like receptors (TLR) maybe impaired in children. For example, an insufficient amount of MyD88 (an adaptor protein involved in TLR signaling) was found in children [16,17].

### Increase in infant mortality rate

There is a high statistically significant correlation between increasing number of vaccine doses and growing infant mortality rates and the percentage of hospitalizations. Based on a study published in 2009, in spite of the United States (US) spending more per capita on health care, the country (with 6.22 infant deaths per 1000 live birth) ranked 34th in order of infant mortality rate and 33 countries such as Singapore, Iceland, Malta, Czech Republic and Cuba ranked higher than the US. In the first five countries such as Singapore (2.31), Sweden (2.75), Japan (2.79), Iceland (3.23) and France (3.33) only 12 vaccine doses and in the US, 26 vaccine doses are given to infants during the first year of life. High rate of infant mortality have been reported between the ages of 2 to 4 months (the highest rate of vaccination) especially when the first doses of DPT vaccine were given to infants [18,19]. Evaluation of a mathematical model of the 2009 H1N1 influenza pandemic in Mexico in six age groups (0-5 yr, 6-12 yr, 13-19 yr, 20-39 yr, 40-59 yr,  $\geq 60$  yr) has revealed that the optimal age groups for vaccination against the disease were young adults (20-39 yr) followed by school age children (6-12 yr) [20].

### Adverse events following immunization (AEFI)

**Excipients:** 1) A few months after Pandemrix<sup>®</sup> (the influenza A vaccine containing the AS03 adjuvant) administration following the influenza A (H1N1) epidemic in Europe, more than 800 children across Europe (especially in Sweden and Finland) have been diagnosed with narcolepsy-cataplexy [21]. At present, assessments of the causal mechanisms about the adjuvant remains to be investigated and long term epidemiological studies about AS03-adjuvanted influenza A (H1N1) pandemic vaccine prepared with the European inactivation/purification protocol are recommended [22].

2) Aluminum adjuvants are neurotoxin and associated with a set of autoimmune/inflammatory disorders [23] and autism [24]. These adjuvants should not be used as placebos in clinical trial studies [25].

3) Autistic spectrum disorder [26] and psychomotor development deficit [27] have been reported with thimerosal containing vaccines. It was indicated that the instantaneous relative excess mercury that the US children received from vaccines ranged from 11 to 150-fold in comparison to the US Environmental Protection Agency (EPA) safety guidelines and 2.7 to 37-fold in comparison to the US Food and Drug Administration (FDA) safety guidelines for the oral ingestion of methylmercury at a given age [28]. Nevertheless, the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) emphasize the safety of thimerosal and continued use of thimerosal-containing vaccines [29,30].

**Vaccines:** 1) Vaccine-associated paralytic poliomyelitis (VAPP) and vaccine-derived polioviruses (VDPV) are the serious outcomes of the administration of live oral poliovirus vaccine (OPV), because all live attenuated strains of OPV can mutate or revert to neurotropic form [31]. The risks of these disorders was considerably increased after the OPV administration and OPV cessation and transition from OPV to inactivated poliovirus vaccine (IPV) is necessary in order to reduce the risk of VAPP and the dangers of outbreaks associated with VDPV [32]. OPV has not been used in the US since 2000 and it was discontinued in New Zealand in 2002. Afterwards, no VAPP has been reported in the US [33].

2) During the swine flu pandemic in 1976, the influenza A (H1N1)/New Jersey/1976 vaccine was administered to 45 million people in the US, but the vaccination campaign was suspended after 10 weeks because of increased cases of Guillain-Barré syndrome [34]. In 2003, 27 years later, the Institute of Medicine concluded that: "people who received the 1976 swine influenza vaccine had an increased risk for developing Guillain-Barré syndrome but the exact reason for this association remains unknown" [35]. New investigations revealed that influenza A (H1N1) vaccine was associated with the risk of Guillain-Barré syndrome [36].

### Deep distrust to vaccination campaigns

In 2011, the Central Intelligence Agency (CIA) organized a fake vaccination program against hepatitis B virus (HBV) in a poorer part of Abbottabad (Pakistan) to obtain Osama bin Laden's children DNA to provide evidence that the family was present. Genetic material retrieved from his infant relatives during vaccination would have been compared to a DNA sample from the brain of Bin Laden's sister who died of cancer in Boston in 2010. In order to organize the vaccination campaign, the CIA enlisted a Pakistani doctor, Shakil Afridi, who has since been arrested by the Inter-Services Intelligence agency of Pakistan for cooperating with American intelligence agents. The project evidently failed, but the violation of trust threatens to set back global public health efforts by decades. After three years, Lisa Monaco, a counterterrorism and homeland security adviser to President Obama, in response to a January 2013 letter signed by the deans of 12 public health schools that sharply criticized the CIA's use of a vaccination campaign (such programs have prompted attacks on medical workers in Pakistan), wrote in a letter that: "the CIA would no longer use immunization programs - or workers - as a means to collect intelligence, no DNA or genetic material would be used and the CIA policy applied worldwide and to U.S. and non-U.S. persons alike" [37-39].

### Inefficacy of vaccines

Vaccines do not provide complete or permanent protection against infectious diseases.

On the basis of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) data published in 2011, unvaccinated children in two of the three age groups under investigation (1-5 and 11-17 yr versus 5-10 yr) showed fewer infections and atopic disorders than those who were vaccinated. The study compared the health outcomes of unvaccinated children versus vaccinated children which were conducted from May 2003 to May 2006 by the Robert Koch Institute [40].

Despite a high coverage rate with two doses of mumps-containing vaccine, the largest mumps outbreak in two decades occurred in the

US. Of the 133 patients with investigated vaccine history in Iowa, 87 (65%) had documentation of receiving two doses and 19 (14%) one dose of mumps-containing vaccine [41].

### Vaccines contamination

The FDA recommended suspension in the use of Rotarix<sup>®</sup> due to contamination with porcine circovirus 1 (PCV1) DNA [42]. Victoria et al. examined the purity of a number of human attenuated viral vaccines. The sequence analysis revealed the unexpected viral sequences of retrovirus avian leukosis in the measles vaccine (Attenuvax<sup>®</sup>), low level of a virus similar to simian retrovirus in RotaTeq<sup>®</sup> and significant levels of PCV1 in Rotarix<sup>®</sup> [43].

### Polyvalent vaccines risks

A rise to the possible association between administration of hexavalent vaccines and sudden unexplained infant death (SUID) has been reported [44] and according to the CDC report, increased or unexpected deleterious health effects are the results of mixed exposures to chemical substances and other stressors [28].

### Role of national health care systems

Repevax<sup>®</sup> is recommended by the United Kingdom National Health Service for pregnant women immunization against pertussis and consists of nine various antigens including: diphtheria, tetanus, pertussis and poliomyelitis (produced in Vero cells), aluminum phosphate, phenoxyethanol and polysorbate 80. It is stated in the factsheet: "This says that the vaccine is not recommended for use in pregnancy because of the routine exclusion of pregnant women from clinical trials and not because of any specific safety concerns or evidence of harm in pregnancy. Use in pregnancy is not contraindicated" [45].

But the manufacturer of the vaccine, Sanoufi Pasteur, has explicitly specified in the package leaflet: "Tell your doctor or nurse if you or your child is pregnant or breast-feeding, think you or your child might be pregnant or planning to have a baby. Your doctor or nurse can advise you whether or not vaccination should be delayed. The use of REPEVAX<sup>®</sup> is not recommended during pregnancy" [46].

The manufacturer statement about side effects and adverse events of the vaccine: "Some additional adverse events have been reported in the various recommended age groups during the commercial use of REPEVAX<sup>®</sup>. The frequency of these adverse events cannot be precisely calculated, as it would be based on voluntary reporting in relation to the estimated number of vaccinated persons [46].

There is one main conclusion to be drawn from the above statements: No well-controlled studies (for example, post marketing surveillance studies) have assessed the adverse events following immunization with this vaccine in pregnant women and the safety of the vaccine (as cited in the factsheets) in pregnancy is in disagreement.

### Deceptive advertising

More than 120 types of human papillomavirus (HPV) have been identified and they are classified as: low-risk viruses (Lr-HPV), probable high-risk viruses (pHr-HPV) and high-risk viruses (Hr-HPV) that the latter cause precancerous lesions and cancer, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 [47]. Cervical cancer takes years to develop and HPV infection does not

necessarily mean cervical cancer. Most HPV infections are transient and will clear completely from the body within 2 years [48].

There are two HPV vaccines, Gardasil<sup>®</sup> and Cervarix<sup>®</sup>. Both vaccines protect against infection with the types of high-risk HPV (types 16 and 18); Gardasil<sup>®</sup> also protects against infection with the two types of low-risk HPVs (types 6 and 11) that cause genital warts.

It seemed that some of advertising campaign slogans of Gardasil<sup>®</sup> manufacturer, Merck, such as: "Your daughter could become one less life affected by cervical cancer" and "Boys can be affected by HPV disease too" designed to exaggerate the danger of HPV infections and cervical cancer to promote vaccination with Gardasil<sup>®</sup>.

### HPV vaccination facts

1) Gardasil<sup>®</sup> and Cervarix<sup>®</sup> do not prevent infection with all HPV types that may cause cervical cancer and the vaccines are not used to treat HPV infection, abnormal cervical cells, or cervical cancer. These vaccines protect against infection with HPV types 16 and 18 (2 types from 15 types of Hr-HPV).

2) Gardasil<sup>®</sup> enhances cervical disease (a greater number of cervical intraepithelial neoplasia grade 2/3, CIN 2/3) in individuals who had HPV infection with vaccine-relevant HPV types (16 and 18) prior to vaccination. CIN 2/3 is considered to be precursors to cervical cancer [49].

3) Current HPV vaccines do not protect against all HPV types that cause cervical cancer and women who have received the HPV vaccines, still need regular cervical screening. In other words, vaccination is not a substitute for routine cervical cancer screening and it is important for vaccinated women to continue to undergo routine cervical cancer screening [50].

4) Type replacement is defined as: elimination of some viral types causing an increase in incidence of other types and can occur naturally during infection or by vaccination. Mass vaccination with HPV types targeted by vaccines, can change the distribution of infection with other types of HPVs. For example, Choi et al. reported an increase of 3-10% in long-term cervical cancer incidence due to non-vaccine HPV types following vaccination [51].

5) Studies have shown that infections with multiple types (coinfections) of HPV can occur (samples with three, four, or five genotypes were also seen and these different genotypes are not necessarily high-risk HPV types 16 and 18) and seem to act synergistically in cervical carcinogenesis [52]. On the other hand, HPV infections are type and age-specific. For instance, a research in the US showed that both cytological abnormalities and Hr-HPV infections with types 16 and 18 decreased with increasing age [53] and in other investigations, HPV type 45 was present chiefly in Colombian women under 50. Type and Age-specific HPV prevalence and multiple types infections can influence vaccine impact and highlight the role of HPVs other than types 16 and 18 [54].

6) HPV is a necessary but not sufficient cause of all cervical cancers, and other cofactors are necessary for progression from cervical HPV infection to cervical cancer. These cofactors include: younger age at first full-term pregnancy and number of full-term pregnancies, number of sexual partners, body mass index, younger age at first intercourse, long-term hormonal contraceptive use [55], tobacco smoking [56], other sexually transmitted coinfections such as herpes simplex virus-2 (HSV-2) [57], *Chlamydia trachomatis* [58], human immunodeficiency virus (HIV) [59], male circumcision [60], diet and

nutrition [61] and occupation [62]. As can be seen, various cofactors are involved in development and progression of cervical cancer after primary HPV infection.

## Evaluation of hepatitis B vaccination as an example

### Transmission/exposure of hepatitis B virus:

- From infected mother to her newborn at birth
- Unprotected sex and through of body fluids, such as semen and vaginal fluids
- Sharing IV drug needles, syringes, or other drug-injection equipment
- Living in a household with an infected person
- Sharing earrings, razors and toothbrushes with an infected person
- Unsterilized needles, including tattoo or piercing needles
- Direct contact with an infected person blood [63-64]

Glancing at the routes of transmission, except from mother to newborn and living with an infected person, HBV cannot transmit to infants by other routes of exposure. In the US, the CDC recommends routine screening of all pregnant women for hepatitis B virus surface Antigen (HBsAg) and in case of infected pregnant women; hepatitis B vaccine and hepatitis B immune globulin (HBIG) are administered after birth [65]. The incidence rates of acute hepatitis B are highest among adults; especially males aged 25-44 years [66].

**Duration of protection and booster vaccination:** In the 1980s, duration of protection of hepatitis B vaccine was optimistically predicted for ten years but the results of various researches showed shorter duration of protection and different immune responses among vaccinated individuals. For example, protection periods from 5 yr (one-third failed to response to a booster dose) [67] to 15 yr [68] have been reported. In spite of the differences in immune responses between newborns and adults and considering maximum reported duration of protection (15 yr), booster vaccination is necessary when vaccinated individuals reach puberty. Accordingly, booster vaccination is recommended [69].

**Serious and chronic side effects of hepatitis B vaccine:** Just like other vaccines, this vaccine also has side effects but some of them are chronic which cannot be cured or rather do not have definite treatments. For example, autism [70], systemic lupus erythematosus [71], Guillain-Barré syndrome [72] and multiple sclerosis [73]. Guillain-Barré syndrome and multiple sclerosis have been mentioned as the side effects in the leaflets of three hepatitis B vaccine manufacturers (ENGERIX<sup>®</sup>-B, HBVAXPRO<sup>®</sup> and RECOMBIVAX HB<sup>®</sup>) whereas the WHO considers that the complete data do not support a causal relationship between hepatitis B vaccine and the mentioned side effects [74].

**Statistics for hepatitis B vaccine adverse events:** Due to the main database of vaccines adverse events in the US is the Vaccine Adverse Events Reporting System (VAERS), in next part, some possible errors of this system will be evaluated.

1) From 1991 to 1998, a total 1771 neonatal adverse reactions and 18 cases of death were reported to VAERS. For 18 cases of neonatal death, the mean age of neonates at vaccination was 12 days (age range, 1-27 days), the median time from vaccination to onset of symptoms was 2 days (range, 0-20 days) and median time from onset of

symptoms to death was 0 day. After autopsy, the causes of 12 cases were reported sudden infant death syndrome (SIDS) [75].

It should be noted that the occurrence of SIDS is rare during the first month of life and its peak is 2-3 months after birth [76] and in order to diagnosis of SIDS or sudden unexplained death in childhood (SUDC) a complete autopsy with trained specialist, a uniform federal law, a suitable and standard questionnaire for the interview with parents of SIDS victims and referral centers for performing autopsies are required [77]. In the US, the first autopsy protocol was published in 1976 but since March 1, 2006 taking the vaccination history is required in new sudden unexplained infant death investigation (SUIDI) reporting form and according to the Soldatenkova and Yazbak research, a systematic review of neonatal SIDS and other unexpected infant deaths following the first dose of hepatitis B vaccination should be done at the international level [78].

2) Principally, monitoring of vaccine safety for various reasons including occurrence of rare but serious adverse reactions after widespread use, multivalent vaccination, errors in reporting of side effects and simultaneous incidence of several side effects is complicated. For these reasons, establishment of a vaccine safety monitoring system (in the US, VAERS and Vaccine Safety Datalink (VSD) have established) in order to study possible risks of vaccines and performing an effective post marketing surveillance program is essential, but the interpretation of data from such databases is complex and is associated with substantial uncertainty [79]. For example, 2% of adverse reactions are reported to VAERS [19]. This under-reporting highlights the limitations of the passive systems in exact evaluation of incidence of adverse events following immunization. Meranus et al. by performing a survey study in the US, indicated that 17% of respondents (composed of 60 commercial vaccinator employees and school health nurses, 500 physicians and 300 pharmacists) would not know how to report an adverse event, 61% of respondents citing unclear definitions of a reportable adverse event and 18% of respondents unaware of whose responsibility it is to report an adverse event. The response rate was 36% [80].

3) If an adverse event appears immediately or a few days after vaccine administration, it is reported by parents or physicians but in the case of long term adverse events (e.g., after a few weeks or months), there is differing view on the subject and these events are never reported for lack of parental awareness about delayed types of adverse reactions of vaccines.

In 2011, a survey study was performed with 1745 Canadian parents in order to investigate parents' knowledge, awareness, attitudes and behaviors related to immunization by telephone. The study showed 4.24% (74 from 1745) of parents sought medical attention for their child as a result of a reaction to medication and only 0.23% (4 from 1745) of them said that their child became ill (including seizures, vomiting, diarrhea, flu, shortness of breath and eye irritation) in the days following the vaccination [81].

4) Randomized clinical trials (because of limited volunteers and relative short durations) [82] cannot detect long term adverse events and risk of an adverse event in population that not exposed to the vaccine. Accordingly, spontaneous reports and results of randomized clinical trials do not provide sufficient data for vaccine safety databases [83]. On the other hand, vaccines are biological products and adverse events for a particular vaccine may vary from one manufacturer to another [84] and batch to batch variation in vaccine manufacturing is still remained a problem [85]. For these reasons, post marketing

surveillance, follow up of medical reports and computerized claims databases for detection of possible new, unusual and rare vaccines adverse events, change in the frequency of known ones and in order to determine patient risk factors for special types of adverse events are essential [82-83].

## Hepatitis B Vaccination and Hepatocellular Carcinoma

The most important reason for immediately after birth hepatitis B vaccination is the WHO recommendation that states: "If infection is observed combined with Hepatitis B virus at very low age, the probability of chronic disease and as a result appearances of long term complications such as Cirrhosis or Hepatocellular Carcinoma (HCC) increases during adulthood" [86].

**Risk factors of HCC:** HCC is the sixth most common cancer in the world and the third common cause of death from cancer. Annually, HCC is the cause of the 600000 deaths worldwide that almost half of them are in China [87]. HCC risk factors include: cirrhosis [88], Aflatoxins [89], hemochromatosis [90], alcohol consumption [91], diabetes [92], tobacco smoking [93], overweight and obesity [94], severe  $\alpha$ 1-antitrypsin deficiency [95], anabolic steroids [96], oral contraceptives [97] and chronic hepatitis B or C [87-90, 92, 96].

**Global increase of HCC:** It was proved that HCC is increasing worldwide, For example, in the United States [98] and southern Europe [99]. Hepatitis C virus, tobacco smoking, heavy alcohol consumption and obesity are responsible for the increasing trend of HCC in these regions [100,101].

In Asia and Africa, HBV infection is the main risk factor of HCC [102] but the role of other HCC risk factors cannot be ignored. For instance, Hepatitis C virus, alcohol consumption and overweight in Japan [103], hepatitis C virus, alcohol consumption and aflatoxins in India [104] and aflatoxins in sub-Saharan Africa and Asia [105] have been reported as other important risk factors of HCC.

**Hepatitis B vaccination and HCC protection:** The results of a 20-yr follow up study in Taiwan (1983-2004 and ages 10-29 yr) showed that the 50% of the vaccinated children were developed HCC despite the complete immunoprophylaxis with the vaccine (vaccine failure); in other words, even administration of complete hepatitis B vaccination could not protect a half of children from HCC. Also, HCC incidence rate was highly statistically significant in 20 years or older full vaccinated individuals. According to the research, current vaccination program could not prevent mother-to-child transmission of HBV and improvement of the HBIG administration during the first 24 hours after newborn birth should be performed [106]. Because of the current hepatitis B immunization program failures to prevent hepatitis B maternal transmission (which can lead to HCC development) [107] and vaccine failure, HBIG administration or antiviral therapy have been the focus of attention [108]. Also, a globally special attention on behavior modifying, improving individual education, exact testing of all blood donations and assuring asepsis in clinical practice is needed to reduce the infection rate of HBV in the world [109].

Briefly, considering the HBV routes of exposure, need to booster vaccination and short duration of protection, insufficient data obtained from clinical trials about chronic and serious side effects of the vaccine, the importance and the role of other HCC risk factors, vaccine failure to prevent HCC and the fact that humans are the known reservoirs of HBV, except mother-to-child exposure and living with someone who has a HBV infection, screening of pregnant women in order to identify

at risk newborns is completely safer than routine newborns vaccination immediately after birth and postpone of HBV vaccination until puberty is quite rational.

## Conclusion

In an overview of the all above mentioned issues, because of: (i) the differences between the immune systems of newborns/children and adults, (ii) death, serious and chronic side effects due to excipients or active ingredients of vaccines, (iii) vaccine failure and inadequate quality control of vaccines, (iv) risks of polyvalent vaccines, and (v) a profit-seeking approach to vaccination, changing the age of vaccination from infancy/childhood to adolescence/adulthood is necessary. In order to achieve public confidence in immunization and success of vaccination programs, the following activities should be performed: (i) retrospective and prospective studies to reassess safety, efficacy, quality and protection duration of vaccines in infants and children worldwide, (ii) proper implementation of good clinical practice and prospective studies to investigate chronic side effects of vaccines in the world, (iii) establishment of a globally network and vaccine safety database by collaboration of international organizations and institutions, vaccine manufacturers, national regulatory authorities and vaccine research academic centers of all countries for sharing and exchange of information and experiences about vaccines quality control, safety and efficacy, (iv) new researches and investigations to choose safer excipients and more efficient formulation of vaccines, and (v) enhancement of awareness and knowledge of healthcare professionals and people about immunization and its related issues by governments.

## Disclaimer

The opinions, interpretations and conclusions expressed in the paper are the private views of the author and do not necessarily represent the views of the Pasteur Institute of Iran as a vaccine manufacturer. The information was obtained from publicly available sources, including published literatures and regulatory documents.

## Conflict of Interest

The author declares that there is no conflict of interest.

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