Vaccine 37 (2019) 366–371

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Causal relationship between immunological responses and adverse reactions following vaccination

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ARTICLE INFO

Article history:
Received 28 June 2018
Received in revised form 19 September 2018
Accepted 29 September 2018
Available online 30 November 2018

Keywords:
Gelatin allergy
Anaphylaxis
Influenza vaccine
Adverse events
Adverse reaction

ABSTRACT

Vaccine adverse events and controversial safety issues have occurred in recent decades in Japan: aseptic meningitis following the measles-mumps-rubella combined vaccine (MMR), anaphylaxis after immunization with live virus vaccines and inactivated split influenza vaccine, an increased incidence of febrile illness following the simultaneous administration of inactivated vaccines, and chronic pain with neurological illness after immunization with the human papilloma virus vaccine (HPV). Vaccine adverse events are a matter of concern for the public as well as general practitioners; some are within the range of assumptions that adverse reactions after live attenuated vaccines are related to the nature of their parental wild-type viruses. Vaccines stimulate the innate immunity of host immunological defense mechanisms and induce the development of specific acquired immunity. Some adverse events related to autoimmune responses have been reported, such as idiopathic thrombocytopenic purpura and acute disseminated encephalomyelitis (ADEM). Although a plausible relationship was not demonstrated, the possibility of an association cannot be denied. The pathogenicity of adverse reactions was investigated for anaphylactic reactions, systemic and local reactions following vaccinations. Initial innate immune responses are essential for the development of acquired immunity and are related to adverse events from different viewpoints.

Contents

1. Introduction

Vaccine adverse events are a matter of great concern for the general public. Although vaccine adverse events are the events observed following immunization, a plausible relationship has not yet been scientifically demonstrated. Vaccine adverse events include incidental events, and vaccine adverse reactions indicate the events for which a relationship is scientifically explained. In Japan, unfavorable events after vaccinations are registered by the Ministry of Health, Labor and Welfare as vaccine adverse reactions without evaluating the relationship. Therefore, vaccine adverse events are all reported as vaccine adverse reactions. The general public worldwide, not only in Japan, has great concerns about adverse reactions. The misunderstandings associated with vaccine

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https://doi.org/10.1016/j.vaccine.2018.11.045
0264-410X/

adverse reactions need to be clarified in order to investigate the causal relationships between vaccinations and adverse events.

There is a long history of vaccine adverse events. Encephalitis after the smallpox vaccination was a controversial issue in 1960–70 [1], and two accidental deaths after immunization with the whole cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTwP) were reported in 1974/75 [2]. Although a direct relationship to the vaccination was not demonstrated in these cases, they were handled as adverse reactions because of the time course of the events. DTwP was discontinued temporarily and began to be used at ≥ 2 years of age; however, vaccine coverage remained at low levels. The number of patients with pertussis and pertussis deaths increased until the acceptance of the new type of acellular pertussis vaccine that was developed and a combined vaccine (DTaP) was introduced into recommended immunization practice in 1981 [3,4]. After 1981, the number of pertussis patients decreased; however, the recent resurgence of pertussis is a matter of great concern because of the short duration of the vaccine immunity of DTaP [5,6]. The adverse events of this vaccine (DTwP) triggered the development of a new vaccine with less adverse reactions.

Vaccine adverse events and critical events after 1990 are shown in Fig. 1. The measles-mumps-rubella combined vaccine (MMR) was implemented in 1989 but was discontinued in 1993 because of an unexpectedly high incidence of aseptic meningitis due to the mumps vaccine component [7]. Anaphylactic cases were reported after immunization with live vaccines in 1994 [8,9]. Post-marketing activity was enhanced, and serum samples were obtained from patients with allergic illness [10]. Acute disseminated encephalomyelitis (ADEM) was reported after immunization with the mouse brain-derived Japanese encephalitis vaccine and was associated with the potential risk of allergic encephalitis [11]. This prompted the development of a tissue culture-based vaccine that was introduced in 2009 [12]. A higher incidence of febrile illness was observed in young children immunized in the H5N1 pandemic vaccine clinical trial [13]. The *Haemophilus influenzae* type B vaccine (Hib) was licensed in 2008 and the pneumococcus vaccine (PCV) and human papilloma vaccine (HPV) were subsequently introduced. Incidental death was reported in seven young infants immunized with the inactivated vaccine alone or a simultaneous administration with Hib, PCV, or DTaP (Ministry of Health, Labor and Welfare homepage: www.mhlw.go.jp/stf/houdou/2r98520000014ac1.html). Hib and PCV were suspended but were restarted one month later because the incidence of serious adverse events was similar to that reported worldwide. The incidence of fever ≥ 38.0 °C in the concomitant administration group (DPT-hepatitis B vaccine (HBV)-IPV-Hib with PCV7) was significantly higher than that reported in the separate vaccination group, whereas no significant difference was observed in the incidence of fever ≥ 39.0 °C [14]. Similarly, increased febrile illness was observed in subjects immunized with PCV7 simultaneously with/without Hib and/or DTaP. G-CSF levels were higher in serum samples obtained from the recipients with febrile illness within 48 h of simultaneous immunization [15]. Chronic pain with cognitive or neurological disorders was reported in female adolescents immunized with HPV [16]. Most of the reported cases were incidental events and no significant difference was reported between the incidence of these symptoms in subjects immunized with HPV and those without HPV [17]. Vaccine adverse events have occurred over a few decades, with some resulting in a distrust of vaccines due to irresponsible rumors or misunderstandings. Measles and rubella outbreaks occurred in 2007 and 2013, respectively [18,19]. These outbreaks were not vaccine adverse events, but they were associated with an indecisive governmental immunization strategy due to a fear of adverse events.

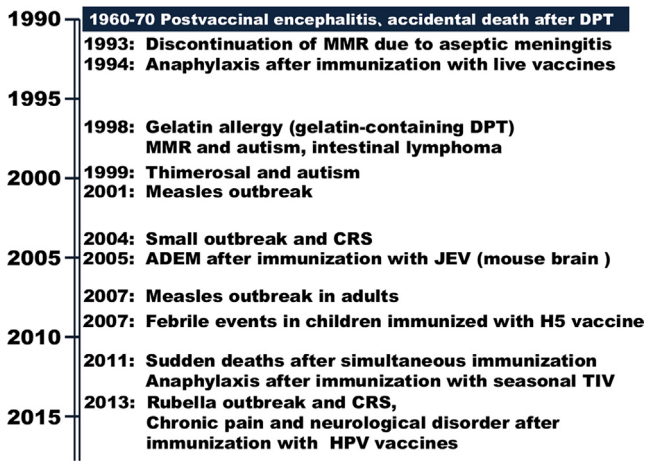

Fig. 1. Vaccine adverse events and critical events after 1990 in Japan. Measles outbreaks in 2001 and 2007 and the outbreak of rubella in 2013 were not adverse events, but associated with an indecisive governmental immunization strategy.

2. Gelatin allergy

An expanded programme on immunization (EPI) implemented the measles vaccination at 9 months of age, and the number of reported cases of measles and vaccine coverage reported by the WHO after the introduction of EPI. The number of laboratory diagnosed measles cases reported was approximately 4 million with less than 20% worldwide coverage of the measles vaccine in 1980 [20]. The number of laboratory confirmed reported cases declined gradually with an increase in vaccine coverage. However, the number of measles patients under 9 months of age did not decrease in developing countries in the late 1980s. Several strategic actions were conducted, and a regular dose of the measles vaccine was administered to young infants < 9 months of age. The standard potency of measles vaccines showed poor immunogenicity when administered to infants < 9 months of age because of the presence of maternal conferred immunity. Clinical trials using several strains with high potency measles vaccines containing 50-100-fold higher infectivity were conducted for infants aged 4–6 months in several developing countries and higher mortality was reported three years later in subjects immunized with high potency vaccines than in those with standard potency [21]. These findings were attributed to other infectious diseases due to the transient immunosuppression of high titered vaccines. However, the standard potency of the AIK-C strain induced a stronger serological response than other high titered measles vaccines and the AIK-C strain was expected for the EPI vaccine in infants < 9 months in developing countries [22,23,24]. These developing countries are in tropical areas without cold-chain system and, thus, temperature stability needs to be improved for tropical use. The measles vaccine licensed in Japan at that time contained 0.2% bovine gelatin but was heat labile and not appropriate for tropical use. Hydrolyzed porcine gelatin was used at 2.0% for the heat-stable measles vaccine. The findings of temperature stability are shown in Fig. 2. The infectivity of the conventional measles vaccine decreased by more than 10^{-2} at 37C for 7 days, whereas reductions in the potency of the heat-stable vaccine containing 2.0% hydrolyzed porcine gelatin was within 10^{-1} drop. The measles vaccine using a new stabilizer was introduced on the market in 1993 and anaphylactic adverse reactions were reported after its introduction. These reactions were initially considered to be due to an egg allergy [25]. Between 1994 and 1997, 366 cases of allergic reactions were reported to the post-marketing research unit of Kitasato Institute

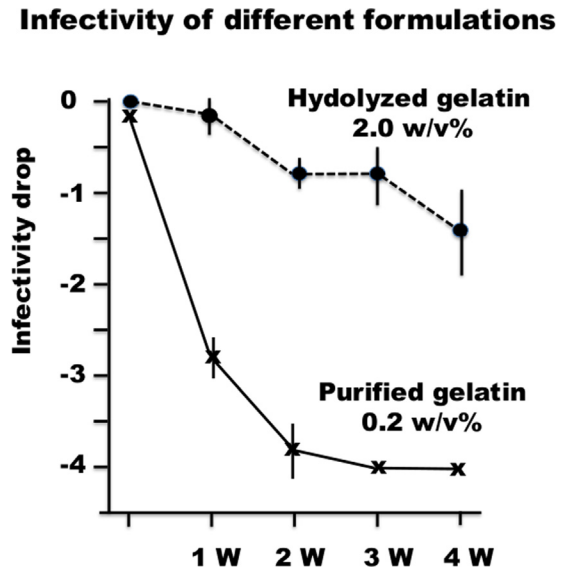

Fig. 2. Heat stability of the measles vaccine. The conventional formulation of the stabilizer was 0.2% of purified gelatin, and 2.0% of hydrolyzed gelatin was used for heat-stable vaccines. Vaccines are kept at 37C and infectivity is measured. Heat stability means that the reduction in infectivity for 7 days at 37C is within 10^{-1}.

and serum samples were obtained from 27 patients with anaphylaxis, 48 with urticaria, 90 with systemic eruptions, 41 with local eruptions, and 29 with non-adverse events. The findings of the IgE antibody against gelatin are shown in Fig. 3. The IgE antibody was detected in 25/27 (93%) cases of anaphylaxis, 27/48 (56%) of urticaria, 8/90 (9%) of systemic eruptions, and none of the local eruptions and controls [8]. As previously reported, anaphylaxis occurred after administration of medicines, such as gelatin-capsulated suppositories, and consumption of confections, such as gelatin-containing jelly, besides inoculation with a live inactivated vaccine, posing a social problem [26]. The mechanism of gelatin sensitization should be elucidated to resolve gelatin allergy.

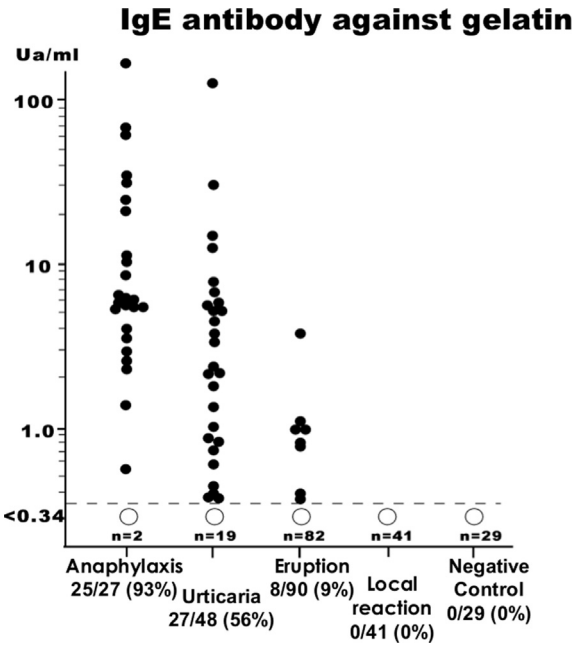

Fig. 3. IgE antibodies in different categories of allergic reactions. Twenty-seven cases of anaphylaxis, 48 of urticaria, 90 of generalized eruption, 41 of local reactions, and 29 of control (from Ref. [8]. J Allergy Clin Immunol 1999; 103:321–5.).

No anaphylaxis had been reported when or before MMR vaccine was used. After the adverse events of DTwP in 1974/75, the DTwP vaccine was recommended for infants of 2 years of age after the measles vaccination. The less reactogenic DTaP was developed in 1981 and the recommended age for the DTaP vaccine gradually shifted to <1 year of age before the measles vaccination during the MMR period. Most patients with anaphylaxis who tested positive for gelatin IgE antibodies had a history of immunization with the gelatin-containing DTaP vaccine. Acellular pertussis showed poor immunogenicity and an alum adjuvant was added. We investigated whether the gelatin-containing DTaP vaccine induced sensitization against gelatin. The IgE antibody against gelatin was detected in 2 out of 103 subjects immunized with gelatin-containing DTaP, but not in 62 subjects immunized with gelatin-free DTaP. Therefore, DTaP showed a causal relationship and the small amount of gelatin with the alum adjuvant promoted its sensitization after being administered three times. Kumagai et al. [27] reported a lymphoproliferative response against gelatin in patients with a gelatin allergy. Pertussis components is sticky in nature and gelatin was used for pre-coating in some devices to prevent the loss of the materials during purification procedures. Gelatin was removed from all DTaP and live vaccines in Japan from 2000, and the number of anaphylactic reactions markedly decreased [9,10].

3. Anaphylaxis after immunization with influenza vaccine

Similar anaphylactic events occurred in 2011/12. Anaphylaxis was reported after immunization with inactivated influenza vaccines using 2-phenoxyethanol (2-PE) as the preservative. Most patients were 3–8 years of age and the incidence of anaphylaxis was estimated to be 1.4 in 100,000 doses in 2011/12 compared with an incidence of <0.4 in 100,000 doses of the other brands [28]. Allergic reactions after vaccination with influenza vaccines were attributed to an egg allergy for a long time; however, the concentration of ovalbumin in influenza vaccines was less than 1 ng/ml [29,30]. The IgE antibody against influenza components was detected in sera obtained from patients with anaphylaxis [31]. How were patients sensitized to the allergen? The presence of the IgE antibody against influenza vaccine was sporadically reported in a small study [32,33]. The influenza split vaccine has theoretically no ligand to the pattern recognition receptors (PRRs) of innate immunity and only induces Th2 responses [34]. A plausible explanation indicated that the presence of the IgE antibody against influenza vaccines developed with yearly immunizations, and the development of the IgE antibody was investigated before and one month after the 1st and 2nd doses in different age groups [35]. The IgE antibody against H1N1, H3N2, and B influenza vaccine components increased among 30% of subjects $\leq$3 years of age after vaccinations and developed at a lower incidence in older children (Fig. 4). The IgE antibody did not develop after natural infection with H1N1 pdm. The split influenza vaccine induces IgE sensitization in young children, particularly those $\leq$3 years of age. The influenza vaccine volume for the inoculation was changed from the 2011/12 season. Prior to the 2011/12 season, the inoculation volume was 0.1 ml for <1-year, 0.2 ml for 1–6 years, 0.3 ml for 6–12 years, and a single dose of 0.5 ml for >13 years. It was amended in volume: two doses of 0.25 ml for <3 years and two doses of 0.5 ml for 3–13 years [35]. The mechanisms responsible for the influence of 2-PE have not been elucidated. It was speculated that the size of antigen particles may have increased slightly during the preservation period. In the following year, 2-PE was replaced with thimerosal as a preservative. The incidence of anaphylaxis returned to that observed in the previous year. Several cases of anaphylaxis are reported every year and, among them, the IgE antibody against influenza vaccine materials was detected. New influenza vaccines need to induce Th1 and Th2 responses.

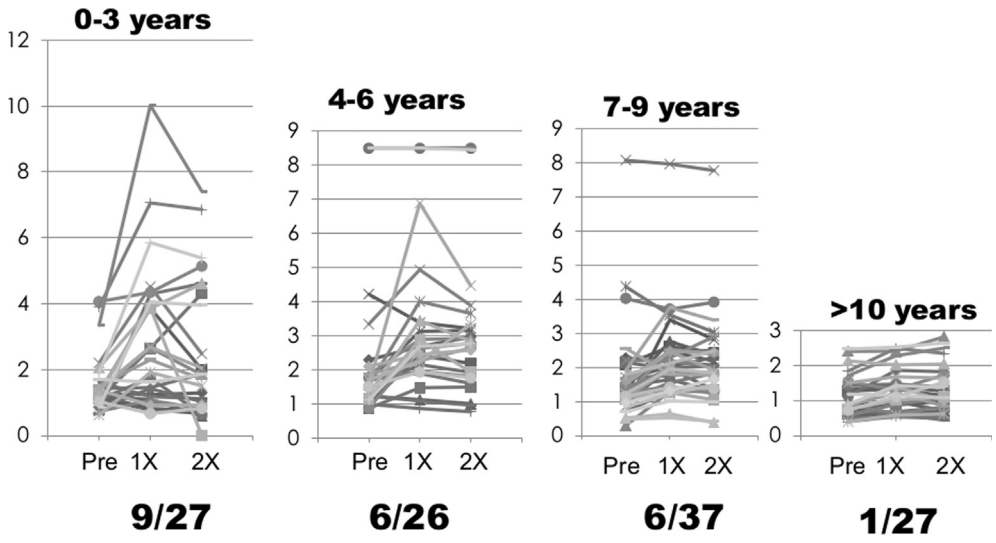

Fig. 4. Development of IgE antibodies against the influenza H1N1 antigen before (Pre) and one month after the first dose (1X) and second dose (2X). The number of significant increases (more than a two-fold increase after vaccination) in IgE antibodies is shown (from Ref. [35]. Vaccine 2015; 33: 6099–105.).

4. Febrile illness after vaccinations with inactivated vaccines

A febrile reaction after vaccinations with inactivated vaccines is a common adverse reaction. The mechanisms responsible for the febrile reaction currently remain unclear. A conventional whole virion-inactivated influenza vaccine and whole cell pertussis vaccine frequently caused febrile adverse reactions within 24 h of the vaccination, and influenza split and acellular pertussis vaccines were developed with a lower incidence of febrile illness [2,3]. The resurgence of H5N1 in 2003 resulted in concerns regarding a potential pandemic. An alum-adjuvanted whole virion-inactivated formulation was developed for the H5N1 pandemic vaccine. High fever $\geq$38 °C was observed in approximately 60% of subjects <3 years. Cytokine production was investigated in peripheral blood mononuclear cells (PBMCs) stimulated with alum alone, the whole virion-inactivated antigen, and adjuvanted whole virion-inactivated antigen, and the alum-adjuvanted vaccine enhanced the production of IL-1β, IL-6, IL-17, IFN-γ, and TNF-α [13]. The production of high levels of inflammatory cytokines was associated with stronger immune responses and a febrile reaction.

After the introduction of Hib and PCV into the recommended routine immunization schedule, seven accidental deaths following simultaneous administration were reported and, thus, these vaccines were temporarily stopped. One month later, they were restarted because the incidence of serious adverse reactions was similar to that reported outside of Japan. However, the mechanisms responsible for the safety of simultaneous administration have not yet been elucidated in detail. A more familiar adverse event was febrile illness and the incidence of high fever increased following simultaneous administration. We obtained 61 serum samples when high fever was noted, 18 without febrile illness after vaccination, and 10 from normal subjects. Although no significant differences were noted in inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, among sera obtained from subjects with or without febrile reactions, a markedly higher level of G-CSF was observed in sera obtained from vaccine recipients with febrile illness after immunization, particularly simultaneous administration, including PCV [15]. The simultaneous administration increased the incidence of febrile illness in the study, and similar findings showed that only PCV7 was associated with an independently increased risk of febrile convulsions, and the risk of febrile convulsions increased when an inactivated influenza vaccine was given concomitantly with a PCV- or DPT-containing vaccine or when all three vaccines were administered together [36].

Human peripheral lymphocytes were stimulated with DPT, Hib, or PCV alone, or a simultaneous stimulation. Cytokine production was investigated in PBMC cultures stimulated with various combinations of inactivated vaccines. High levels of IL-6 were produced when they were stimulated with Hib alone or simultaneously stimulated with DPT and/or PCV. Higher levels of IL-1β, TNF-α, and G-CSF were produced with the simultaneous stimulation [15]. These findings may associate with the increased incidence of febrile illness following simultaneous administration.

Effective vaccines for Hib and PCV were introduced in Japan in 2008 and 2010, respectively, and simultaneous administration was implemented in pediatric general practice. However, the biological mechanisms responsible for the synergistic responses of combined administration currently remain unclear. We need to consider the combination of different types of vaccines to reduce febrile adverse reactions.

5. Adverse reactions of live attenuated vaccines

Live attenuated vaccines have the original biological characteristics of their parental wild-type viruses, implying the possibility of causing illness observed as complications of natural infection. A febrile reaction was noted among 10–15% of recipients within several days of vaccinations with measles-containing vaccines. The incidence of common adverse reactions after immunization with live vaccines depends on the growth of a virus in the body. During virus replication, viral genomic RNA and double-stranded RNA stimulate the innate immune system, resulting in the production of cytokines and chemokines [37]. A biological marker of attenuation is lower viral growth than parental wild-type viruses. The AIK-C measles vaccine strain is a further attenuated live measles strain developed by small plaque cloning at 32.5 °C that exhibits unique biological temperature-sensitive characteristics and small plaque formation: poor or no virus growth at a higher temperature of 39 °C (*ts*). The molecular backgrounds for the attenuation were investigated, generating infectious cDNA of the AIK-C by reverse genetics. Using this system, Pro at the position of 439 amino acid protein of phospho (P) protein was a critical amino acid for the *ts*

phenotype and Leu at the position 278 of the fusion (F) protein was responsible for small plaque formation [38,39].

The live attenuated rubella Takahashi KRT strain was developed at 35 °C in rabbit kidney cells, demonstrating poor or no virus growth at 39 °C. We also developed a reverse genetic system of KRT and a recombinant infectious cDNA analysis showed that His at position 1042 of the p150 region of KRT was responsible for weaker virus growth at 39 °C of the *ts* phenotype [40]. The mumps Hoshino vaccine strain was developed in chicken embryogenic cells at a lower temperature; however, the vaccine strain did not have a strict *ts* phenotype. The only biological marker was small plaque formation in Vero cells and no viral growth in B95a cells. A fusion assay was performed using expression plasmids of the F and HN proteins from the Hoshino vaccine and circulating wild-types. Leu at position 383 of the F protein of the Hoshino vaccine strain induced no fusion on B95a and small plaques in Vero cells, suggesting weaker virus growth [41]. These findings for the molecular mechanisms underlying the development of attenuation are linked to vaccine safety and provide a clearer understanding of vaccine adverse events.

6. Immunological reactions following immunization

Cytokine production in peripheral lymphocyte cultures stimulated with inactivated vaccines and the production of inflammatory cytokines of IL-1β, TNF-α, and G-CSF were observed in lymphocyte cultures stimulated with DTaP, PCV, and Hib. Enhanced production was observed when stimulated with a combination of two or three vaccines [15]. These findings were consistent with an increased incidence of febrile illness, with high levels of G-CSF correlating with febrile illness within 48 h following immunization with inactivated vaccines [15]. These cytokines and G-CSF are related to the reactogenicity and immunogenicity of vaccines [37].

In 2011, two types of HPV vaccines were introduced into routine immunization and were discontinued because of cases of local pain and some of chronic pain in remote regions besides the injection site as well as autonomic nervous disorders [16,42]. Thirty out of 120 patients were diagnosed with vaccine-related symptoms and 42 were suspected of vaccine-related illness, and the time from the vaccination to onset ranged between 1 and 1532 days (average 319.7 ± 349.3 days) [42]. Neurological symptoms developed long after the initial HPV vaccination and are questionable because of the finding of the same symptoms being observed among subjects without immunization with HPV [17]. Hib, PCV, DPT, and HPV vaccines were inoculated into mice and the sequential local production of inflammatory cytokines and G-CSF was investigated [43]. These cytokines were produced from 3 h and peaked 48 h after the immunization of mice with 2-valent HPV combined with adjuvant of alum and monophosphryl lipid A (Cervarix). The production of IL-4, MCP-1, and TNF-α peaked 5 or 7 days after an immunization with alum-adjuvanted 4-valent HPV (Gardasil). These cytokines decreased after 7 days of immunizations with Cervarix and Gardasil and thereafter. Vaccine formulations and adjuvants stimulate the innate immune system and induce the production of inflammatory cytokines and chemokines. Local histological examinations were conducted following immunization in mice, and inflammatory nodules were detected at the injection site of adjuvanted vaccines, but not after non-adjuvanted vaccines [44]. These inflammatory nodules remained for more than 6 months after immunization with decrease in size and no inflammatory reactions being suggested. These findings indicate that local pain at the injection site was closely related to the HPV vaccination, whereas chronic pain was scientifically unexplainable.

7. In summary

We investigated the vaccine adverse events since 1990 in Japan. Two events of anaphylaxis of gelatin allergy and following immunization with influenza split vaccine were related to the IgE sensitization. Anaphylaxis is an extremely rare event and a febrile reaction is a common adverse reaction following immunization. Inflammatory cytokines and G-CSF were detected in subjects with febrile illness and inflammatory responses inducing inflammatory cytokines and G-CSF were also detected at the injection site. Initial innate immune responses are essential for the development of acquired immunity and are related to adverse events from different viewpoints. More detailed knowledge on innate immunity has recently promoted immunological analyses for a better understanding on the development of adaptive immune responses and biomarkers for vaccine safety and immunogenicity.

Acknowledgments

The contents of the study were presented in a lecture for the 12th Takahashi Award at the 21st Annual Meeting of the Japanese Association of Vaccinology. I thank many following pediatricians who participated in the clinical research: Dr. Takuji Kumagai (Kumagai Pediatric Clinic), Dr. Teruo Okafuji and Dr. Takao Okafuji (Okafuji Pediatric Clinic), Dr. Eitaro Suzuki (Suzuki Pediatric Clinic), Dr. Akiko Miyata (Saiwai Children's Clinic), Dr. Takao Nagai (Nagai Pediatric Clinic), Dr. Takao Ozaki (Kohnan Kosei Hospital), Dr. Yasuyo Kashiwagi and Dr. Hisashi Kawashima (Tokyo Medical University), Dr. Kenji Okada (Fukuoka Nursing College), the late Dr. Toshiaki Ihara and the late Dr. Hitoshi Kamiya (National Mie Hospital)

Disclosure statement

The corresponding author T. Nakayama has received research funding from Daiichi Sankyo Pharmaceutical and Kitasato-Daiichi Sankyo Vaccine.

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