Vaccines and Autoimmunity

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Contents

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Introduction

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Vaccines and Autoimmunity is a result of decades of experience in vaccinology, immunology, and autoimmunity, and of a review of the vast literature in this field. The book has three parts. Part I deals with general mechanisms of vaccine- and adjuvant-induced autoimmunity. In Parts II and III, we have asked the different authors to summarize, on one hand, individual vaccines and which common autoimmune diseases they may trigger in susceptible individuals (Part III), and on the other, the common autoimmune diseases and identified vaccines which may trigger their emergence (Part III).

The editors of this book are quite confident that vaccinations represent one of the most remarkable revolutions in medicine. Indeed, vaccines have been used for over 300 years and are probably one of the most effective strategies for preventing the morbidity and mortality associated with infections. Like other drugs, vaccines can cause adverse events, but unlike conventional drugs, which are prescribed to people who are ill, vaccines are administered to healthy individuals, which increases the concern over adverse reactions. Most side effects attributed to vaccines are mild, acute, and transient. Nonetheless, rare reactions, such as hypersensitivity and induction of autoimmunity, do occur, and can be severe and even fatal. In this regard, the fact that vaccines are delivered to billions of people without preliminary screening for underlying susceptibilities is thus of concern (Bijl *et al.*, 2012; Tomljenovic and Shaw, 2012; Soriano *et al.*, 2014).

Indeed, it is naive to believe that all humans are alike. Notably, autoimmune diseases have been increasingly recognized as having a genetic basis, mediated by HLA subtypes. For instance, celiac disease has been strongly associated with HLA haplotype DR3-DQ2 or DR4-DQ8 (Liu *et al.*, 2014), multiple sclerosis with HLA-DRB1 (Yates *et al.*, 2014), rheumatoid arthritis with HLA-DR4 and HLA-DQ8 (Vassallo *et al.*, 2014), and type I diabetes with HLA-DR3/4 (Steck *et al.*, 2014). Thus, certain HLA genes create a genetic predisposition toward development of autoimmune disease, typically requiring some environmental trigger to evolve into a full-blown disease state (Luckey *et al.*, 2011). One such environmental trigger which is commonly associated with development of autoimmunity is viral (Epstein Barr virus, cytomegalovirus, and hepatitis C virus) or bacterial (*Heliobacter pylori*) challenge (Rose, 2010; Magen and Delgado, 2014).

The multifacet associations between infectious agents and subsequent development of autoimmune or autoinflammatory conditions have been well established, and a number of mechanisms by which infectious agents can bring about such responses have been identified (molecular mimicry, epitope spreading, polyclonal activation, and others) (Molina and Shoenfeld, 2005; Kivity *et al.*, 2009; Shoenfeld, 2009; Rose, 2010).

Vaccines and Autoimmunity, First Edition. Edited by Yehuda Shoenfeld, Nancy Agmon-Levin, and Lucija Tomljenovic.

Recently, we and others have suggested another mechanism, namely the adjuvant effect, by which infections may relate to autoimmunity in a broader sense (Rose, 2010; Rosenblum *et al.*, 2011; Shoenfeld and Agmon-Levin, 2011; Zivkovic *et al.*, 2012; Perricone *et al.*, 2013). Adjuvants are substances which enhance the immune response. For this purpose, they are routinely included in vaccine formulations, the most common of which are aluminum compounds (alum hydroxide and phosphate). Although the mechanisms of adjuvancy are not fully elucidated, adjuvants seem to modulate a common set of genes, promote antigen-presenting cell recruitment, and mimic specific sets of conserved molecules, such as bacteria components, thus increasing the innate and adaptive immune responses to the injected antigen (Agmon-Levin *et al.*, 2009; Israeli *et al.*, 2009; McKee *et al.*, 2009; Exley *et al.*, 2010; Perricone *et al.*, 2013).

Although the activation of autoimmune mechanisms by both infectious agents and substances with adjuvant properties (such as those found in vaccines) is common, the appearance of an autoimmune disease is not as widespread and apparently not always agent-specific. The adjuvant effect of microbial particles, namely the nonantigenic activation of the innate and regulatory immunity, as well as the expression of various regulatory cytokines, may determine if an autoimmune response remains limited and harmless or evolves into a full-blown disease. Additionally, as already mentioned, the genetic background of an individual may determine the magnitude of adverse manifestations. For example, it has been shown that the vaccine for Lyme disease is capable of triggering arthritis in genetically susceptible hamsters and that, when the adjuvant aluminum hydroxide is added to the vaccine, 100% of the hamsters develop arthritis (Croke *et al.*, 2000). Other studies have shown that the development of inflammatory joint disease and rheumatoid arthritis in adults in response to the HepA and HepB vaccines, respectively, is correlated to the HLA subtype of the vaccinated individual (Ferrazzi *et al.*, 1997; Pope *et al.*, 1998). Given that aluminum works as an adjuvant by increasing expression of MHC (Ulanova *et al.*, 2001), it perhaps should not be surprising that in individuals susceptible to autoimmune disease on the basis of the MHC, HLA subtype might be adversely affected by the use of aluminum hydroxide in vaccines. In addition to aluminum, the vaccine preservative thimerosal has also been demonstrated to induce a systematic autoimmune syndrome in transgenic HLA-DR4 mice (Havarinasab *et al.*, 2004), while mice with a genetic susceptibility for autoimmune disease show profound behavioral and neuropathological disturbances. These results are not observed in strains of mice without autoimmune sensitivity.

We have recently reported a new syndrome: "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA), which encompasses a spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum, and other adjuvants, as well as infectious components, which may also have an adjuvant effect. All these environmental factors have been found to induce autoimmunity and inflammatory manifestations by themselves, both in animal models and in humans (Israeli *et al.*, 2009; Shaw and Petrik, 2009; Shoenfeld and Agmon-Levin, 2011; Gherardi and Authier, 2012; Israeli, 2012; Cruz-Tapias *et al.*, 2013; Lujan *et al.*, 2013; Perricone *et al.*, 2013).

The definition of the ASIA syndrome thus helps to detect those subjects who have developed autoimmune phenomena upon exposure to adjuvants from different sources. For example, the use of medical adjuvants has become common practice, and substances such as aluminum adjuvant are added to most human and animal vaccines, while the adjuvant silicone is extensively used for breast implants and cosmetic procedures (Kaiser *et al.*, 1990; Molina and Shoenfeld, 2005; Israeli *et al.*, 2009; Shoenfeld and Agmon-Levin, 2011; Cohen Tervaert and Kappel, 2013). Furthermore, "hidden adjuvants" such as infectious material and house molds have also been associated with different immune-mediated conditions associated with the so-called "sick-building syndrome" (Israeli and Pardo, 2010; Perricone *et al.*, 2013).

Although ASIA may be labeled a "new syndrome," in reality it reflects old truths given a formal label (Meroni, 2010). Notably, in 1982, compelling evidence from epidemiological, clinical, and animal research emerged to show that Guillain-Barre syndrome and other demyelinating autoimmune neuropathies (i.e., acute disseminated encephalomyelitis and multiple sclerosis) could occur up to 10 months following vaccination (Poser and Behan, 1982). In such cases, the disease would first manifest with vague symptoms (arthralgia, myalgia, paraesthesia, weakness; all of which are typical ASIA symptoms), which were frequently deemed insignificant and thus ignored by the treating physicians. However, these

symptoms would progress slowly and insidiously until the patient was exposed to a secondary immune stimulus (in the form of either infection or vaccination). This would then trigger the rapid and acute clinical manifestation of the disease (Poser and Behan, 1982). In other words, it was the secondary anamnestic response that would bring about the acute overt manifestation of an already present subclinical long-term persisting disease.

Thus, it was already recognized in the early 1980s that vaccine-related manifestations often presented themselves as unspecific, yet clinically relevant symptoms (termed "bridging symptoms" Poser and Behan (1982) or "nonspecific ASIA symptoms" by us (Shoenfeld and Agmon-Levin, 2011)). These manifestations pointed to a subclinical, slowly evolving disease. Whether this disease would eventually progress to its full-blown clinically apparent form depended on whether the individual was further exposed to noxious immune stimuli, including subsequent vaccinations. As a case in point, we recently described six cases of systemic lupus following HPV vaccination (Gatto *et al.*, 2013). In all six cases, several common features were observed; namely, a personal or familial susceptibility to autoimmunity and an adverse response to a prior dose of the vaccine, both of which were associated with a higher risk of post-vaccination full-blown autoimmunity. Similarly, in an analysis of 93 cases of autoimmunity following hepatitis B vaccination (Zafrir *et al.*, 2012), we identified two major susceptibility factors: (i) exacerbation of adverse symptoms following additional doses of the vaccine (47% of patients); and (ii) personal and familial history of autoimmunity (21%).

It should further be noted that some individuals who are adversely afflicted through exposure to adjuvants do not satisfy all of the criteria that are necessary to diagnose a full-blown and clinically apparent autoimmune disease (Perricone *et al.*, 2013). Nonetheless, these individuals are at higher risk of developing full-blown autoimmunity following subsequent adjuvant exposure, whether that be via infections or vaccinations (Poser and Behan, 1982; Zafrir *et al.*, 2012; Gatto *et al.*, 2013).

A casual glance at the US Centers for Disease Control and Prevention (CDC, 2013)_immunization schedule for infants shows that according to the US prescribed guidelines, children receive up to 19 vaccinations during infancy, many of which are multivalent in the first 6 months of their life (Table I.1).

The various vaccines given to children, as well as adults, may contain either whole weakened infectious agents or synthetic peptides and genetically engineered antigens of infectious agents and adjuvants (typically aluminum). In addition, they also contain diluents, preservatives (thimerosal, formaldehyde), detergents (polysorbate), and residuals of culture growth media (*Saccharomyces cerevisiae*, gelatin, bovine extract, monkey kidney tissue, etc.; Table I.2). The safety of these residuals has not been thoroughly investigated, primarily because they are presumed to be present only in trace amounts following the vaccine manufacture purification process. However, some studies

Table I.1 Typical pediatric vaccine schedule for preschool children currently recommended by the US Centers for Disease Control and Prevention (2013a). Shaded boxes indicate the age range in which the vaccine can be given. Asterisks denote Al-adjuvanted vaccines. Hep A is given in 2 doses spaced at least 6 months apart. According to this schedule, by the time a child is 2 years of age, they would have received 27 vaccinations (3 × HepB, 3 × Rota, 4 × DTaP, 4 × Hib, 4 × PCV, 3 × IPV, 2 × Influenza, 1 × MMR, 1 × Varicella, and 2 × HepA)

Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
HepB*	HepB*			HepB*						
	Rota	Rota	Rota							
	DTaP*	DTaP*	DTaP*			DTaP*			DTaP*	
	Hib*	Hib*	Hib*	Hib*						
	PCV*	PCV*	PCV*	PCV*						
	IPV	IPV		IPV						IPV
						Influenza (yearly)				
				MMR					MMR	
				Varicella					Varicella	
						HepA*				

Hep A, hepatitis A; Hep B, hepatitis B; Rota, rotavirus; DTaP, diphtheria-pertussis-tetanus; Hib, *Haemophilus influenzae* type b; PCV, pneumococcal; IPV, inactivated polio; MMR, measles-mumps-rubella

Table I.2 Complete list of vaccine ingredients (i.e., adjuvants and preservatives) and substances used during the manufacture of commonly used vaccines. Adapted from US Centers for Disease Control and Prevention (2013b)

Vaccine	Vaccine excipient and media summary
DT (Sanofi)	aluminum potassium sulfate, peptone, bovine extract, formaldehyde, thimerosal (trace), modified Mueller and Miller medium
DTaP (Daptacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol, Stainer–Scholte medium, modified Mueller's growth medium, modified Mueller–Miller casamino acid medium (without beef heart infusion)
DTaP (Infanrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer–Scholte liquid medium
DTaP (Tripedia)	sodium phosphate, peptone, bovine extract (US sourced), formaldehyde, ammonium sulfate, aluminum potassium sulfate, thimerosal (trace), gelatin, polysorbate 80 (Tween 80), modified Mueller and Miller medium, modified Stainer–Scholte medium
DTaP-HepB-IPV (Pediarix)	formaldehyde, gluteraldehyde, aluminum hydroxide, aluminum phosphate, lactalbumin hydrolysate, polysorbate 80, neomycin sulfate, polymyxin B, yeast protein, calf serum, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium, Vero (monkey kidney) cells
DTaP-IPV/Hib (Pentacel)	aluminum phosphate, polysorbate 80, formaldehyde, gutaraldehyde, bovine serum albumin, 2-phenoxethanol, neomycin, polymyxin B sulfate, Mueller's Growth Medium, Mueller–Miller casamino acid medium (without beef heart infusion), Stainer–Scholte medium (modified by the addition of casamino acids and dimethyl-beta-cyclodextrin), MRC-5 (human diploid) cells, CMRL 1969 medium (supplemented with calf serum)
Hib (ActHIB)	ammonium sulfate, formalin, sucrose, Modified Mueller and Miller medium
Hib (Hiberix)	formaldehyde, lactose
Hib (PedvaxHIB)	aluminum hydroxphosphate sulfate
Hib/Hep B (Comvax)	yeast (vaccine contains no detectable yeast DNA), nicotinamide adenine dinucleotide, hemin chloride, soy peptone, dextrose, mineral salts, amino acids, formaldehyde, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, sodium borate
Hep A (Havrix)	aluminum hydroxide, amino acid supplement, polysorbate 20, formalin, neomycin sulfate, MRC-5 cellular proteins
Hep A (Vaqta)	amorphous aluminum hydroxyphosphate sulfate, bovine albumin, formaldehyde, neomycin, sodium borate, MRC-5 (human diploid) cells
Hep B (Engerix-B)	aluminum hydroxide, yeast protein, phosphate buffers
Hep B (Recombivax)	yeast protein, soy peptone, dextrose, amino acids, mineral salts, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, formaldehyde
Hep A/Hep B (Twinrix)	formalin, yeast protein, aluminum phosphate, aluminum hydroxide, amino acids, phosphate buffer, polysorbate 20, neomycin sulfate, MRC-5 human diploid cells
Human Papillomavirus (HPV) (Cerverix)	vitamins, amino acids, lipids, mineral salts, aluminum hydroxide, sodium dihydrogen phosphate dehydrate, insect cell and viral protein
Human Papillomavirus (HPV) (Gardasil)	yeast protein, vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, sodium borate
Influenza (Afluria)	beta-propiolactone, thimerosol (multi-dose vials only), monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, neomycin sulfate, polymyxin B, egg protein
Influenza (Fluarix)	sodium deoxycholate, formaldehyde, octoxynol-10 (Triton X-100), α-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), hydrocortisone, gentamicin sulfate, ovalbumin
Influenza (Fluvirin)	nonylphenol ethoxylate, thimerosal (multidose vial–trace only in prefilled syringe), polymyxin, neomycin, beta-propiolactone, egg proteins
Influenza (Flulaval)	thimerosal, α-tocopheryl hydrogen succinate, polysorbate 80, formaldehyde, sodium deoxycholate, ovalbumin
Influenza (Fluzone: standard, high-dose, & intradermal)	formaldehyde, octylphenol ethoxylate (Triton X-100), sodium phosphate, gelatin (standard formulation only), thimerosal (multidose vial only), egg protein
Influenza (FluMist)	ethylene diamine tetraacetic acid (EDTA), monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gentamicin sulfate, egg protein

Table I.2 (*Continued*)

Vaccine	Vaccine excipient and media summary
Meningococcal (MCV4Menactra)	formaldehyde, phosphate buffers, Mueller Hinton agar, Watson Scherp media, Modified Mueller and Miller medium
Meningococcal (MCV4Menveo)	formaldehyde, amino acids, yeast extract, Franz complete medium
Meningococcal (MPSV4Menomune)	thimerosal (multidose vial only), lactose, Mueller Hinton agar, Watson Scherp media
MMR (MMR-II)	vitamins, amino acids, fetal bovine serum, sucrose, sodium phosphate, glutamate, recombinant human albumin, neomycin, sorbitol, hydrolyzed gelatin, chick embryo cell culture, WI-38 human diploid lung fibroblasts
MMRV (ProQuad)	sucrose, hydrolyzed gelatin, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium phosphate dibasic, neomycin, bovine calf serum, chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells
Pneumococcal (PCV13 – Prevnar 13)	casamino acids, yeast, ammonium sulfate, Polysorbate 80, succinate buffer, aluminum phosphate
Polio (IPV – Ipol)	2-phenoxyethanol, formaldehyde, neomycin, streptomycin, polymyxin B, monkey kidney cells, Eagle MEM modified medium, calf serum protein
Rabies (Imovax)	albumin, neomycin sulfate, phenol, MRC-5 human diploid cells
Rabies (RabAvert)	β-propiolactone, potassium glutamate, chicken protein, ovalbumin, neomycin, chlortetracycline, amphotericin B, human serum albumin, polygeline (processed bovine 14 gelatin)
Rotavirus (RotaTeq)	sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, fetal bovine serum, vero cells (DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq; PCV-1 and PCV-2 are not known to cause disease in humans)
Rotavirus (Rotarix)	amino acids, dextran, sorbitol, sucrose, calcium carbonate, xanthan, Dulbecco's Modified Eagle Medium (DMEM) (Porcine circovirus type 1 (PCV-1) is present in Rotarix; PCV-1 is not known to cause disease in humans)
Td (Decavac)	aluminum potassium sulfate, peptone, formaldehyde, thimerosal, bovine muscle tissue (US sourced), Mueller and Miller medium
Td (Tenivac)	aluminum phosphate, formaldehyde, modified Mueller–Miller casamino acid medium without beef heart infusion
Td (Mass Biologics)	aluminum phosphate, formaldehyde, thimerosal (trace), ammonium phosphate, modified Mueller's media (containing bovine extracts)
Tdap (Adacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol, ammonium sulfate, Mueller's growth medium, Mueller–Miller casamino acid medium (without beef heart infusion)
Tdap (Boostrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80 (Tween 80), Latham medium derived from bovine casein, Fenton medium containing a bovine extract, Stainer–Scholte liquid medium
Typhoid (inactivated – Typhim Vi)	hexadecyltrimethylammonium bromide, phenol, polydimethylsiloxane, disodium phosphate, monosodium phosphate
Typhoid (oral – Ty21a)	yeast extract, casein, dextrose, galactose, sucrose, ascorbic acid, amino acids
Varicella (Varivax)	sucrose, phosphate, glutamate, gelatin, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, sodium phosphate monobasic, EDTA, residual components of MRC-5 cells including DNA and protein, neomycin, fetal bovine serum, human diploid cell cultures
Yellow Fever (YF-Vax)	sorbitol, gelatin, egg protein
Zoster (Shingles – Zostavax)	sucrose, hydrolyzed porcine gelatin, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, neomycin, potassium chloride, residual components of MRC-5 cells including DNA and protein, bovine calf serum

suggest that even these trace amounts may not be inherently safe, as was previously assumed (Moghaddam *et al.*, 2006; Rinaldi *et al.*, 2013).

What is obvious, nonetheless, is that a typical vaccine formulation contains all the necessary biochemical components to induce autoimmune manifestations. With that in mind, our major aim is to inform the medical community regarding the various autoimmune risks associated with different vaccines. Physicians need to be aware that in certain individuals, vaccinations can trigger serious and potentially disabling and even fatal autoimmune manifestations. This is not to say that we oppose vaccination, as it is indeed an important tool of preventative medicine. However, given the fact that vaccines are predominantly administered to previously healthy individuals, efforts should be made to identify those subjects who may be at more risk of developing adverse autoimmune events following vaccine exposure. In addition, careful assessment should be made regarding further vaccine administration in individuals with previous histories of adverse reactions to vaccinations. The necessity of multiple vaccinations over a short period of time should also be considered, as the enhanced adjuvant-like effect of multiple vaccinations heightens the risk of post-vaccine-associated adverse autoimmune and inflammatory manifestations (Tsumiyama *et al.*, 2009; Lujan *et al.*, 2013). Finally, we wish to encourage efforts toward developing safer vaccines, which should be pursued by the vaccine manufacturing industry.

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