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Bullous Pemphigoid Following HBV Vaccine: from Case Reports to a Mosaic of Molecular Evidence.

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Abbreviations: ABD (Autoimmune bullous disease), BP (Bullous pemphigoid), ELISA (Enzyme-linked immunoassay), HBsAg (Hepatitis B virus surface antigen), HBV (Hepatitis B virus), IgG (Immunoglobulin G), Hib (Haemophilus influenzae type b), HLA (Human leukocyte antigen), HHV-6 (Human herpesvirus 6), IPV (inactivated poliomyelitis).

Introduction

Pemphigus stems from the Greek '*pemphix*', which means bubble, encompasses a heterogeneous group of autoimmune blistering diseases which affect both mucous membranes and the skin [1]. Bullous pemphigoid (BP), represents the most common autoimmune bullous disease and mostly affects the elderly, being rare among pediatric population [2]. The disease pathogenesis is related to IgG autoantibodies directed against two structural components of the hemidesmosome, a multiprotein complex of the dermal-epidermal junction providing structural adhesion between basal keratinocytes and dermal extracellular matrix, named BP180 (transmembrane glycoprotein) and BP 230 (hemidesmosomal inner plaque protein). In addition, IgE autoantibodies are also involved in the disease pathogenesis and could be detected in serum and/or skin of those patients using, immunoblot/immunoprecipitation, immunofluorescence studies, and enzyme-linked immunoassay (ELISA) analyses [3].

The destruction of the epidermal adhesion complexes (desmosomes) of keratinocytes leads to acantholysis, a phenomena characterized by the loss of cell–cell adhesion, resulting in intra-epidermal blistering and the clinical appearance of flaccid blisters and erosions at involved sites [4]. Unlike adults, the clinical presentation amongst children turns to have greater acral involvement with predominance of palmoplantar lesions, sparing the mucosa and genital area. Indeed, palmoplantar lesions are considered as a diagnostic clue of infantile BP. Schwieger-Briel, *et al*. proposed the following minimal diagnostic criteria: typical clinical presentation and linear IgG and/or C3 deposition at the basement membrane in immunofluorescence microscopy studies [5].

Although a clear trigger is not well established, it has been recognized that a combination of genetic predisposing factors, as class II HLA (e.g., HLA-DQβ1*0301), and environmental influences, such as vaccines, viral infections, diet, neoplasms, and drugs, may

contribute to the loss of immune tolerance [1,6]. Infantile BP has usually a good prognosis and resolves quite rapidly after initiation of treatment [7]. Along the years, growing incidence of autoimmune diseases after vaccination have been reported specially, among children. Postvaccination BP is an idiopathic disorder that has been predominantly associated with tetanus, diphtheria, pertussis, hepatitis, influenza and polio vaccine alone or in combination with other vaccines [4,8]. Almost 15 years after our first case report of pemphigus following a hepatitis B virus vaccination [10], we now describe another similar case which in addition to a panoply of published cases, unites a plausible etiologic association. In this article, we portray a case report of a four-month old female patient who presented with a new onset of BP following the second inoculation with HBV HBsAg vaccine, providing the molecular explanation laying behind this correlation.

Case Report

A four-month old female patient, presented with a new onset of BP, which appeared three months following her second inoculation with HBV HBsAg vaccine. During the appearance of her rash she also received her second dose of hexavalent INFANRIX™ IPV/Hib vaccine (directed against diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b), developing afterwards irritability, mild-fever, and a predominant palm-plantar rash which in the subsequent days adopted the typical blister form of the BP disease.

Discussion

We present a case of a four-month old female patient who appeared with a new onset pemphigus following HBV vaccination. Interestingly, the initial symptoms characterized by irritability, mild-fever, and a predominant palm-plantar rash started three months after the vaccination. In the meanwhile, the patient received a second dose of the hexavalent INFANRIX™ IPV/Hib vaccine and progressed to the typical BP disease blistering rash over the subsequent days.

Could the BP disorders have been caused by autoimmune cross-reactions triggered by vaccines? And, if so, by which of the vaccines? The HBV HBsAg vaccine, the INFANRIX™ IPV/Hib hexavalent vaccine, or both of them?

Epidemiological evidence

Experimental investigations have hinted at a possible role of infections, in particular herpes virus (Cytomegalovirus, Epstein-Barr virus, HHV-6) infections, as well as hepatitis B and C viruses, Toxoplasma gondii, and Helicobacter pylori in the pathogenesis of BP [3,6,11,12]. Viruses can induce autoimmune diseases in several, and not mutually exclusive, ways: (1) new antigens may derive from the incorporation of fragments of the cell membrane into the envelope of the virus, (2) the damage to infected cells, a virus may insert, expose, modify, or release antigens usually hidden, (3) the virus may share epitopes with its host, thus leading to the development of cross-reactive autoantibodies (molecular mimicry) [11,13,14]. The HBV is renowned for its association with induction of autoimmune phenomena [15]. An alluring study performed by Sagi et al., addressed the question whether infectious agent may contribute to the development of autoimmune bullous disease (ABD), including HBV. Interestingly, a significant titer increase in ABD patients when compared with matching controls, and 35% of ABD patients had circulating HBcAb compared with 7% of controls ($p<0.001$) [16].

Over the last decade, wide number of reports emerged linking BP disease with vaccines, mainly affecting pediatric population. Most cases of infantile BP have been described after first dose of vaccination [17]. A retrospective analysis achieved by Erbagci, reported 50 cases of BP following immunization. Of those, 13 patients (10 adults and 3 infants) have been related to various vaccines and tetanus toxoid booster [9]. Further, *Neri et al.* divulged 21 patients with infantile BP related to vaccine administration. Among those children, gender proportion was similar with a mean age at presentation of 3.5 months. The latency period from vaccination to clinical manifestation was 7.5 days (range from 5 hours to 3 weeks) [18]. More recently, a retrospective study performed by *Schwieger-Briel et al*. refer to more than 80 BP cases in children within the first year of life, occurring from 1977 to 2014. Of those, 30.8% had been vaccinated within days or weeks prior to the onset of disease, with the standard mix of passive vaccines recommended in this age group [5].

To date, we have no knowledge of a large randomized controlled trial able to supply concrete data on the incidence of BP among HBV-vaccinated individuals compared with controls.

Clinical evidence

The associated vaccine most often involved with autoimmunity is the HBV vaccine, and its autoimmune side effects have been the subject of many studies in the last decade [10]. The association between HBV vaccine and autoimmunity is temporal only, and no certain causality has been proven. The vaccine or its adjuvant might

induce a non-specific activation of immune system and unmask already existent but dormant pemphigus or alternatively, the vaccine may provoke an autoimmune response [19]. Despite all, it is difficult to acknowledge whether the observation of post-vaccination BP is a coincidental or there is a causal relationship, although this disease is extremely rare over pediatric population [13,20]. Therefore, assorted unanswered questions arise, since most of the cases address to previously healthy children, neither with relevant family history, nor with other knowing predisposing factors. In that line, and to allow a more comprehensive overview, we examined the available clinical reports regarding BP following HBV vaccine or polyvalent formulas containing HBV (Table 1).

Gender/ Age	Vaccines	Latency period	Rash location	Treatment	Recurrence	Ref.
M / 3m	Hexavalent	1w	Palmoplantar	IVIG	No	7
M / 3.5m	Tetracoq	1d	Palmoplantar, face and trunk	Systemic steroids	No	8
F / 12y	HBV	1w	Palmoplantar, extremities, face and trunk	Azathioprine + Systemic steroids	No	9
F / 2m	HBV DPT	2d	Palmoplantar, extremities and face	Oral prednisolone	No	39
F / 5m	Hexavalent Pneumococcus	2w	Palmoplantar and extremities	Symptomatic	No	40
M / 5m	HBV Tetracoq Hib	1w	Palmoplantar, extremities and trunk	Systemic steroids	No	40
M / 5m	HBV Tetracoq Hib	1w	Palmoplantar, extremities and trunk	Systemic steroids	No	40
F / 4m	HBV Tetracoq Hib Meningococcus C	1d	Palmoplantar, face and trunk	Systemic steroids	No	41
F / 2m	Hexavalent	1w	Palmoplantar	Systemic steroids	Yes (after 2º dosis)	12
F / 3m	HBV Tetracoq Hib Meningococcus C Pneumococcus	3w	Palmoplantar, trunk and retroauricular	Systemic steroids	Yes	42
F / 3m	HBV Tetracoq Pneumococcus	2w	Palmoplantar, extremities and trunk	Topical high-potency steroids	No	43
M / 3.5m	HBV Poliomyelitis DPT	2m	Palmoplantar, face and trunk	IVIG	No	44
F / 3m	HBV Hexavalent	3m	Palmoplantar			-

Table 1: *Cases of infantile bullous pemphigoid following vaccination involving HBV.*

(d: days; DPT: Diphtheria, Tetanus, Pertussis; F: female; HBV: Hepatitis B virus; Hexavalent: Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B and Haemophilus influenzae type b; Hib: and Haemophilus influenzae type b; IVIG: intravenous immunoglobulin; M: male; m: months; Tetracoq: Diphtheria, Tetanus, Pertussis, Poliomyelitis; y: years).

When analyzing the evidence of the BP development following the administration of monovalent or multivalent hepatitis B vaccines, several interesting aspects worth to mention: (1) case reports started to pop-up in the literature around 2005, surrounding the decade when the HBV vaccine was implemented as part of required immunization programs over the world; (2) the disorder affected previously healthy children, referring to no other risk factors for disease development; (3) the timing from the inoculation to the clinical manifestations ranged from 1 day to 3 months, which is appropriate for induction of immune response by the vaccine; (4) although it is difficult to point a finger to a single vaccine, there might be synergic(s) mechanism(s) in between to induce autoimmunity; (5) the recurrence of symptoms following a second dose vaccination supports the association; (6) all the patients presented palmoplantar blistering and the response to corticosteroid therapy was generally successful.

Clearly, autoimmunity does not develop in most individuals receiving HBV vaccine, and the infectious trigger represents merely one piece of a complex puzzle, alongside multiple variables, both 'innate' (e.g., genetic background) and 'acquired' (e.g., environmental factors), which together serve as the platform for the development of autoimmune disorders [21,22]. In this context, the reports of post-vaccination autoimmunity events are extremely relevant, as it suggests a genetic predisposition for autoimmunity [13,23]. Nonetheless, the described BP case series as well other assorted autoimmune diseases related to vaccines seem to bloom a plausible connection, justifying further research.

Molecular evidence

HBV vaccines are considered the first efficient vaccines against a major human cancer, including liver cancer among children [24]. The vaccine has been associated mainly with autoimmune neuromuscular disorders, including optic neuritis, Guillain-Barré syndrome, multiple sclerosis, among others such as systemic lupus erythematosus, arthritis, vasculitis, and antiphospholipid syndrome [25]. Immune mediated diseases arise from various different sources: environmental, genetic, hormonal and immune defects, the so called "mosaic of autoimmunity" [26,27]. Infectious agents are considered to be the most common triggers of autoimmunity, and vaccines that contain antigens from infectious agents might induce autoimmunity by similar mechanisms such as yeast antigens, epitope spreading, bystander activation, polyclonal activation, and molecular mimicry [25,28-30]. Other components of vaccines (adjuvants) might also provoke adverse events by stimulation of the immune system, without having any specific antigenic effect of their own [9,21,31,32]. The potential adverse events related to VHB vaccine were explained in detail by Kanduc et al., in which mechanisms involving peptide sharing between the HBsAg and the human proteome, and it potential cross-reactivity in association with the clusters of peptides shared between HBsAg and crucial human proteins, played essential roles [33].

Embracing the intention of elucidate the pathway linking BP with the VHB vaccine, we performed a molecular analysis of the vaccine compounds and compared it with human proteome. As previously described, BP is an autoimmune disease characterized by autoantibodies against two self-antigens: BP230 and BP180. Both self-antigens are part of the hemidesmosomes, which belong to the dermo-epidermal adhesion complexes that promote the adhesion in the epithelium (skin and mucous) [34]. Hence, autoreactive T and B cells from BP patients recognize epitopes clustered in distinct regions of BP180 and BP230 [35]. At molecular level, the specific question is whether the anti-HBV immune response triggered by HBV HBsAg vaccine can also hit the BP autoantigens and disrupt the skin and mucous integrity. The answer is positive, as delineated in Table 2, specifying a sequence analyses document in which HBV vaccine shares three peptides with the self-antigen BP180, whilst no matches were found with the BP230. The peptide sharing reported in Table 2 has a high immunologic potential since the three shared peptides are also present in epitopes that have been experimentally validated as immuno-positive and are catalogued at the IEDB Database. The synopsis of such immunoreactive epitopes are reported on Table 3. In addition, further sequence analyses show that two pentapeptides (GGSSS, TTTST) out of the three, are also present in Bordetella pertussis and Haemophilus influenzae (Table 4). The facts clearly indicate that administration of the hexavalent INFANRIX™ IPV/Hib vaccine following inoculation with HBV HBsAg vaccine could add to the cross-reactivity burden and exacerbate the attack against BP180, implementing the consequent bullous disorder.

Autoantigen	Pentapeptides shared with HBsAg
BP180	GGSSS, GSSSG, TTTST
BP230	-

Table 2: *Peptide sharing between BP autoantigens and HBV HBsAg vaccine.*

IEDB ID	EPITOPE
9760	dprvrglylpaGGSSSGtv
17255	fpaGGSSSGtvnpvlttasp
21221	glyfpaGGSSSGtvn
24655	hqtlqdprvrglylpaGGSSSGtvnp
38393	lpaGGSSSGtvnpapniash
47757	pgsTTTSTgpcktc
53925	rglyfpaGGSSSG
56394	rvrglyfpaGGSSSGtvn
61964	sTTTSTgpcktcttpaqgnsmfpsc
67869	vcplipgsTTTSTgpcktcttpaqg
70730	vrglyfpaGGSSSGtvnp
70731	vrglyfpaGGSSSGtvnpvl
70732	vrglylpaGGSSSGtvnp

value=0.104), -2log likelihood=2517.141, OR= odds ratio, UOR= Unadjusted odd ratio, CI= Confidence interval,

[a]*includes richer and richest,* [b]*includes poorer and poorest,* [c]*private hospital/nursing home, private clinic, other private sector, NGO sector, FPAN, maries topes, other NGO facilities,* [d]*includes public sector, government hospital, primary health care center, health post/sub health post, primary health care outreach clinic, other public sector ,* [e]*includes India and others*

Explore the associated factors of wasting by multivariate analysis

Those children from province 3 were 93.8% (AOR=0.062, 95% CI=0.008-0.478) and those from province 4 were 88.1% (AOR= 0.119, 95% CI=0.027-0.526) to be protect from malnourished (wasted) as compare to those children who live in province 1. Likewise, those children from Tarai were around 4 time (AOR=3.762, 95% CI=1.366-10.365) more likely to be wasted than those children who were live in Mountain. Other religion (Muslim, Terai and other) religion were around 2 time (AOR=1.917, 95% CI=1.133-3.242) more likely to be wasted as compare to Hindu. Those children who had low birth weight were 2.63 times (AOR=2.626, 95% CI=1.556-4.432) more likely to be wasted as compared to those children who were normal (table 2).

Variables	P Value	UOR	Adjusted OR (95% C.I)
Province			
Province-1		1	
Province -2	0.793	1.199	0.926 (0.521-1.66)
Province-3	0.008	0.043	0.062 (0.008-0.478)
Province-4	0.005	0.089	0.119 (0.027-0.526)
Province-5	0.118	0.706	0.627 (0.349-1.127)
Province-6	0.898	0.644	0.953 (0.456-1.989)
Province-7	0.983	0.734	0.993 (0.532-1.856)
Ecological zone			
Mountain		1	
Hill	0.084	1.625	2.369 (0.889-6.454)
Terai	0.010	3.992	3.762 (1.366-10.365)
Religion			
Hindu		1	
Buddhist	0.477	0.342	0.580 (0.129-2.600)
Others f	0.015	2.422	1.917 (1.133-3.242)
Birth weight			
Normal		1	
Low birth weight	<0.001	2.616	2.626 (1.556-4.432)

Table 2: *Predictors of wasted by multivariate analysis.*

1-Reference Category, Cox and snell R square=0.051, Nagelkerke R Square=0.112, Hosmer and Lemeshow test=8.146 (p value=0.419), -2log likelihood=958.42, OR= odds ratio, UOR= Unadjusted odd ratio, CI= Confidence intervals,

[f] *includes Muslim, Terai and other religion*

Explore the associated factors of Underweight by multivariate analysis

With the new federal state, province was found to be significantly associated with underweight. Those U5 Children who were from province 6 were 2 times (AOR=2.076, 95% CI=1.356-3.176) more likely to be underweight than those children from province 1. Regarding the place of residence, rural children were 1.2 times (AOR=1.286, 95% CI= 1.042-1.588) more likely to be underweight compared to children residing in urban areas. Likewise, education level of the mother was also found to be significantly associated with the underweight. Those children from mothers with no education and primary education were 2 times (AOR= 2.016, 95% CI= 1.371-2.964) and 1.5 times (AOR= 1.3535, 95% CI=1.026-2.294) more likely to be underweight respectively compared to those children from mother of higher education. Regarding wealth index, those children from poorer wealth index were nearly 2 times (AOR= 1.757, 95% CI=1.321-2.336) more likely to be underweight compared to children from richer wealth index. Birth weight was also found to be strong predictor for underweight. Those children who were born with low weight were nearly 2 times (AOR=1.976, 95% CI= 1.397-2.796) more likely to be underweight compared to those children who were born with normal weight. From the ethnicity, those children from Brahmin/Chhetri were 1.3 times (AOR=1.383, 95% CI=1.027-1.864) and children from other castes such as Muslim, other Terai caste were almost 2 times (AOR=1.995, 95% CI= 1.356-2.936) more likely to be underweight respectively compared to Janajaties (table 3).

INFANRIX™ IPV/Hib	Pentapeptide component
Poliovirus	-
Bordetella pertussis	TTTST
Clostridium tetani	-
Haemophilus influenzae	GGSSS TTTST
Corynebacterium diphtheriae	-

Table 4: *Occurrences of pentapeptides common to HBsAg and BP180 in the INFANRIX vaccine.*

A possible solution based on unique peptide vaccines

In light of the mentioned body of evidence, it seems that current vaccines may hold a significant risk for developing autoimmune phenomena in susceptible individuals. However, the value of vaccine is not debatable, and the benefits of hepatitis B prevention far outweigh the risk of autoimmune diseases. Nevertheless, would it be possible to eliminate the risk of vaccines while maintaining the benefits? A novel suggestion to this ideal question lies in modifying the pathogenic content of vaccines [13,36]. Current vaccines are composed infectious agent proteins bearing significant similarity to human proteome, and it is possible to select those agents proteins that are unique and carry no similarity to the human proteins [37]. Eventually, by imposing this selectiveness over vaccines would be possible to achieve an effective immune response that will prevent infection, while avoiding the potential cross-reactivity phenomena that may lead to the development of autoimmunity [38].

Conclusion

The benefits of hepatitis B prevention far outweigh the risk of autoimmune diseases. However growing data supports the association between vaccines and autoimmune phenomena, as we illustrate in this article trough the example of BP and HVB vaccine. Indeed, vaccination might trigger an enhanced autoimmune response in patients with a relevant immunologic predisposition or with a subclinical BP. Mechanisms involving peptide sharing between the HBsAg and the human proteome, and potential cross-reactivity in association with the clusters of peptides shared between HBsAg and crucial human proteins, played essential roles. HBV vaccine shares three peptides with the self-antigen BP180, which are also present in epitopes that have been experimentally validated as immuno-positive. In addition, two pentapeptides out of three, are also present in Bordetella pertussis and Haemophilus influenzae. Hence, the administration of the hexavalent INFANRIX™ IPV/Hib vaccine following inoculation with HBV HBsAg vaccine could add to the cross-reactivity burden and exacerbate the attack against BP180, implementing the consequent bullous disease. Although it does not occur in all patients, the possibility of recurrence with subsequent vaccinations must be taken into account. In the light of this knowledge, it emerges the devoir of using the principle of peptide uniqueness as a new paradigm for safe and efficacious vaccinology.

Conflict of interest: Professor Yehuda Shoenfeld appears as a medical consultant in vaccine compensation court, USA. The other authors have no potential conflicts of interest in authorship or publication.

References

1. Kasperkiewicz, M. et al. Pemphigus. Nat. Rev. Dis. Prim. 3, 17026 (2017).
2. Amber, K. T., Murrell, D. F., Schmidt, E., Joly, P. & Borradori, L. (2018). Autoimmune Subepidermal Bullous Diseases of the Skin and Mucosae: Clinical Features, Diagnosis, and Management. Clinical Reviews in Allergy and Immunology. 54(1): 26-51
3. Genovese, G. et al. (2019). New Insights Into the Pathogenesis of Bullous Pemphigoid: 2019 Update. Front. Immunol. 10, 1506.
4. Didona, D., Maglie, R., Eming, R. & Hertl, M. (2019). Pemphigus: Current and Future Therapeutic Strategies. Front. Immunol. 10, 1418.
5. Schwieger-Briel, A. et al. (2014). Bullous pemphigoid in infants: characteristics, diagnosis and treatment. Orphanet J. Rare Dis. 9, 185.
6. Bagci, I. S., Horvath, O. N., Ruzicka, T. & Sardy, M. (2017). Bullous pemphigoid. Autoimmun. Rev. 16, 445–455.
7. Ister, M., Pouessel, G., Ythier, H., Catteau, B. & Carpentier, O. (2014). Postvaccinal, corticosteroid-resistant bullous pemphigoid in infancy: treatment with intravenous immunoglobulin. Pediatr. Dermatol. 31, e94-5.
8. Baykal, C., Okan, G. & Sarica, R. (2001). Childhood bullous pemphigoid developed after the first vaccination. J. Am. Acad. Dermatol. 44, 348–350.
9. Erbagci, Z. (2002). Childhood bullous pemphigoid following hepatitis B immunization. J. Dermatol. 29, 781–785.
10. Berkun, Y., Mimouni, D. & Shoenfeld, Y. (2005). Pemphigus following hepatitis B vaccination--coincidence or causality? Autoimmunity 38, 117–119.

11. Lo Schiavo, A. et al. (2013). Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. Clin. Dermatol. 31, 391–399.
12. Mérida, C., Martínez-Escribano, J. A., Frías, J. F., Sánchez-Pedreño, P. & Corbalán, R. (2005). Penfigoide ampolloso en lactante tras vacunación. Actas Dermosifiliogr. 96, 255–257.
13. Segal, Y. & Shoenfeld, Y. (2018). Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cellular and Molecular Immunology.
14. Shamriz, O. & Shoenfeld, Y. (2018). Infections: a double-edge sword in autoimmunity. Curr. Opin. Rheumatol. 30, 365–372.
15. Ichiki, Y. et al. (2005). T cell immunity in hepatitis B and hepatitis C virus infection: implications for autoimmunity. Autoimmun. Rev. 4, 82–95.
16. Sagi, L. et al. (2011). Autoimmune bullous diseases the spectrum of infectious agent antibodies and review of the literature. Autoimmun. Rev. 10, 527–535.
17. Hafiji, J., Bhogal, B., Rytina, E. & Burrows, N. P. (2010). Bullous pemphigoid in infancy developing after the first vaccination. Clin. Exp. Dermatol. 35, 940–941.
18. Neri, I. et al. (2016). Bullous pemphigoid in infant post vaccination: Myth or reality? Int. J. Immunopathol. Pharmacol. 29, 295–299.
19. Zafrir, Y., Agmon-Levin, N., Paz, Z., Shilton, T. & Shoenfeld, Y. (2012). Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases. Lupus 21, 146–152.
20. Watad, A. et al. (2017). Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) - An update. Lupus 26, 675–681.
21. Bragazzi, N. L., Watad, A., Amital, H. & Shoenfeld, Y. (2017). Debate on vaccines and autoimmunity: Do not attack the author, yet discuss it methodologically. Vaccine.
22. Watad, A. et al. (2019). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: Insights from an analysis of 500 cases. Clin. Immunol. 203, 1–8.
23. Ryabkova, V. A. et al. (2019). Lethal immunoglobulins: Autoantibodies and sudden cardiac death. Autoimmunity Reviews.
24. Shepard, C. W., Simard, E. P., Finelli, L., Fiore, A. E. & Bell, B. P. (2006). Hepatitis B virus infection: epidemiology and vaccination. Epidemiol. Rev. 28, 112–125.
25. Agmon-Levin, N., Paz, Z., Israeli, E. & Shoenfeld, Y. (2009). Vaccines and autoimmunity. Nat. Rev. Rheumatol. 5, 648–652.
26. Vera-Lastra, O., Medina, G., Cruz-Dominguez, M. D. P., Jara, L. J. & Shoenfeld, Y. (2013). Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum. Expert Rev. Clin. Immunol. 9, 361–373.
27. Soriano, A., Nesher, G. & Shoenfeld, Y. (2015). Predicting post-vaccination autoimmunity: who might be at risk? Pharmacol. Res. 92, 18–22.
28. Molina, V. & Shoenfeld, Y. (2005). Infection, vaccines and other environmental triggers of autoimmunity. Autoimmunity 38, 235–245.
29. Kivity, S., Agmon-Levin, N., Blank, M. & Shoenfeld, Y. (2009). Infections and autoimmunity--friends or foes? Trends Immunol. 30, 409–414.
30. Perricone, C. & Shoenfeld, Y. (2013). Hepatitis B vaccination and undifferentiated connective tissue disease: another brick in the wall of the autoimmune/inflammatory syndrome induced by adjuvants (Asia). Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 19, 231–233.
31. Sfriso, P. et al. (2010). Infections and autoimmunity: the multifaceted relationship. J. Leukoc. Biol. 87, 385–395.
32. Guimaraes, L. E., Baker, B., Perricone, C. & Shoenfeld, Y. (2015). Vaccines, adjuvants and autoimmunity. Pharmacol. Res. 100, 190–209.
33. Kanduc, D. & Shoenfeld, Y. (2016). From HBV to HPV: Designing vaccines for extensive and intensive vaccination campaigns worldwide. Autoimmunity Reviews.
34. Kayani, M. & Aslam, A. M. (2017). Bullous pemphigoid and pemphigus vulgaris. BMJ 357, j2169.
35. Thoma-Uszynski, S. et al. (2006). Autoreactive T and B Cells from Bullous Pemphigoid (BP) Patients Recognize Epitopes Clustered in Distinct Regions of BP180 and BP230. J. Immunol. 176, 2015 LP – 2023.
36. Kanduc, D. et al. (2015). Applying the Concept of Peptide Uniqueness to Anti-Polio Vaccination. J. Immunol. Res. 2015, 541282.
37. Lucchese, G., Calabro, M. & Kanduc, D. (2012). Circumscribing the conformational peptide epitope landscape. Curr. Pharm. Des. 18, 832–839.
38. Kanduc, D. (2009). 'Self-nonself' peptides in the design of vaccines. Curr. Pharm. Des. 15, 3283–3289.

39. Bisherwal, K., Pandhi, D., Singal, A. & Sharma, S. (2016). Infantile Bullous Pemphigoid Following Vaccination. Indian Pediatr. 53, 425–426.
40. Guerra, L. et al. (2018). Infantile bullous pemphigoid following vaccination. European journal of dermatology : EJD 28, 708–710.
41. de la Fuente, S. et al. (2013). Postvaccination bullous pemphigoid in infancy: report of three new cases and literature review. Pediatr. Dermatol. 30, 741–744.
42. Valdivielso-Ramos, M., Velázquez, D., Tortoledo, A. & Hernanz, J. M. (2011). Penfigoide ampolloso infantil en relación con la vacunación hexavalente, meningococo y neumococo. An. Pediatría 75, 199–202.
43. Barreau, M. et al. (2012). [Infantile bullous pemphigoid]. Ann. Dermatol. Venereol. 139, 555–558.
44. Xiao, T., Li, B., Wang, Y.-K., He, C.-D. & Chen, H.-D. (2007). Childhood bullous pemphigoid treated by i.v. immunoglobulin. J. Dermatol. 34, 650–653.