



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

Abdulla Wata^{a,b,c}, Nicola Luigi Bragazzi^d, Dennis McGonagle^c, Mohammed Adawi^e, Charlie Bridgewood^c, Giovanni Damiani^{f,g}, Jaume Alijotas-Reig^{h,i}, Enrique Esteve-Valverde^{h,j}, Mariana Quaresma^k, Howard Amital^{a,b}, Yehuda Shoenfeld^{a,b,l,*}

^a Department of Medicine 'B' and Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel

^b Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^c Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

^d Postgraduate School of Public Health, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

^e Padeh and Ziv Hospitals, Azrieli Faculty of Medicine, Bar-Ilan University, Ramat Gan, Israel

^f Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Unità Operativa di Dermatologia, IRCCS Fondazione Ca' Granda, Ospedale maggiore Policlinico, Milano, Italy

^g Clinical Dermatology, Department of Biomedical, Surgical and Dental Sciences, Istituto Ortopedico Galeazzi, University of Milan, 20126 Milan, Italy

^h Unit of Systemic Autoimmune Diseases, Internal Medicine Service, University Hospital Vall d'Hebron, Barcelona, Spain

ⁱ Department of Medicine, Faculty of Medicine, Universitat Autònoma, Barcelona, Spain

^j Internal Medicine Service, Althaia, Xarxa Assistencial de Manresa, Manresa, Barcelona, Spain

^k Department of Medicine A, Centro Hospitalar do Porto, Porto, Portugal

^l Laboratory of the Mosaics of Autoimmunity, Saint Petersburg University, Saint Petersburg, Russian Federation

ARTICLE INFO

Keywords:

ASIA syndrome
International syndrome registry
Vaccines
Foreign material
Silicone breast implants

ABSTRACT

Background: We investigated the pattern of reported immune diseases in the international ASIA syndrome registry.

Methods: Data from 500 subjects exposed to adjuvants from the ASIA syndrome international registry were analysed.

Results: The patient mean age was 43 ± 17 years and 89% were female. Within the reported immune diseases, 69% were well-defined immune diseases (autoimmune, autoinflammation, and mixed pattern diseases). Among the well-defined immune diseases following the exposure to adjuvants, polygenic autoimmune diseases were significantly higher than autoinflammatory disorders (92.7% vs 5.8%, respectively, $p < 0.001$). Polygenic autoimmune diseases such as connective tissue diseases were significantly linked to the exposure to HBV vaccine (OR 3.15 [95%CI 1.08–9.23], $p = 0.036$). Polygenic autoinflammatory diseases were significantly associated with the exposure to influenza vaccination (OR 10.98 [95%CI 3.81–31.67], $p < 0.0001$).

Conclusions: Immune conditions following vaccination are rare, and among these, polygenic autoimmune diseases represent the vast majority of the well-defined immune diseases reported under the umbrella ASIA syndrome. However, vaccines benefit outweighs their autoimmune side effects.

1. Introduction

The term autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first coined in 2011 with the aim of codifying a

growing number of disorders characterised by innate and adaptive immune system dysregulation after adjuvant exposure [1]. The term adjuvant denotes several substances that drive innate immune system pattern recognition receptor (PRR) activation and are commonly used

* Corresponding author at: Zabłudowicz Center for Autoimmune Diseases, Tel-Aviv University, Israel.

E-mail address: shoenfel@post.tau.ac.il (Y. Shoenfeld).

<https://doi.org/10.1016/j.clim.2019.03.007>

Received 7 March 2019; Received in revised form 18 March 2019; Accepted 24 March 2019

Available online 25 March 2019

1521-6616/© 2019 Elsevier Inc. All rights reserved.

in vaccines to boost immune reactivity towards antigens [2,3]. Many substances beyond vaccine adjuvants such as liquid paraffin, silicone gel, acrylamides, hyaluronic acid, and methacrylate compounds have adjuvant properties [4–6]. Aluminium is the most commonly incorporated adjuvant into vaccines and, after many years of widespread use, contrasting data on its toxicity and immune adverse events have been reported [7,8]. Nevertheless, over the last decade, a number of case reports and series reported that vaccines containing aluminium adjuvant might occasionally be associated with serious immunological adverse events including autoimmune diseases [9–11].

Autoimmune diseases are fundamentally linked to aberrant B and T cell dysfunction against self-antigens that result from a complex interplay between genetic background and environmental triggers such as infection, dysbiosis, drugs or adjuvants [12–14]. However, the resulting self-directed inflammation with loss of tolerance, and the induction of immune reactions against self-antigens is relatively rare [15]. Of note, the vast majority of people who are exposed to different adjuvant subtypes do not develop autoimmune phenomena.

It is now widely accepted that at the population level, many diseases viewed as autoimmune actually have a predominantly innate immune mediated or autoinflammatory based pathology such as inflammatory bowel disease or polymyalgia rheumatica (PMR) [15]. It is further recognised that diseases previously viewed as autoimmune including psoriasis and allied seronegative arthropathies are intermediate innate-adaptive overlap disorders [32]. Therefore, an immune disease can be classified as autoimmune or autoinflammatory condition and according to the genetic involvement, each can be stratified into monogenic or polygenic disease.

In order to better understand the link between the different adjuvant subtypes and the spectrum of inflammation against self, an international registry of ASIA syndrome was created in 2011 [16]. A preliminary analysis of 300 patients in 2016 showed that most of the ASIA syndrome patients were female and had a mean age of 38 years. Furthermore, the most commonly reported disease was undifferentiated connective tissue disease (UCTD), found in 26% of the cases [16].

Thus, the aim of the previous study was to increase the awareness of existing conditions that may emerge following the exposure to an adjuvant although a cause-effect relationship is debatable due to the paucity of the described clinical cases, a lack of precise temporal-causal link, and the multitude of exposures to suspected adjuvants. In the current study, we performed an updated analysis of the registry by adding all the cases accumulated between April 2016 and January 2019, giving a total of 500 cases of ASIA syndrome. We also explored the relationship between different immune-mediated disease subtypes (autoimmune *versus* autoinflammation or intermediate diseases) following the exposure to the various adjuvants.

2. Material and methods

2.1. Instrument

An *ad hoc* structured questionnaire, developed to collect all data relevant to ASIA syndrome, was administered to rheumatologists and internists worldwide, as previously described [16]. The cases were uploaded into the registry between 2011 and 2019 February.

2.2. Population: patient inclusion and exclusion criteria

Five hundred and sixty-one patients were reported and inserted in the ASIA registry; 61 cases were excluded due to one or more of the following reasons: i) they did not fulfil the inclusion criteria (meeting one major criterion or one minor and one major) [1], ii) having missing data or insufficient details, iii) when the adjuvant was considered to have no biological plausibility (no experimental models to support the link between the suspected adjuvants and the induction of the well-defined autoimmune condition) iv) when the period between the

disease onset and adjuvant exposure was over 5 years, v) non-specific self-limited reactions within few days after vaccination (e.g. fever, arthralgia and myalgia). Thus, the final cohort consisted of 500 patients with ASIA syndrome.

2.3. Measures (autoimmune, autoinflammation and mixed pattern diseases)

We stratified the well-defined immune mediated diseases into polygenic autoimmune diseases, polygenic autoinflammatory and mixed pattern diseases according to McGonagle et al. immune diseases classification proposed in 2006 [15]. The latter defines an autoimmune self-directed inflammation as a disorder where B and T cell are the main players, the disease initiates in primary and secondary lymphoid organs leading to loss of tolerance, with development of immunity against self-antigens and autoantibodies may predate the clinical disease by several years [15]. On the other hand, autoinflammatory disorder is where local factors at the tissue target resulted in innate immune system mediated tissue damage [15]. Diseases with MHC-class I associations including psoriasis and allied disorders that also show a propensity for tissue specific injury and disease expression were designated as mixed pattern diseases (intermediate diseases). Where a clearly well-defined immune diagnosis was not possible according the criteria above, we classified into undefined immune disorder.

2.4. Statistical analysis

Data related to symptoms, main clinical manifestations, antibody profile status, and diagnosed autoimmune diseases were downloaded from the website and transferred to an *ad hoc* Excel spreadsheet. Before proceeding with any data handling and manipulation, figures were visually inspected for capturing potential outliers. Continuous variables were computed as mean \pm standard deviation, whereas categorical parameters were expressed as percentages, where appropriate. Student's *t*-test, chi-squared test, and analysis of the variance were employed to look at comparisons among the different subgroups of the studied ASIA cohort. All statistical analyses were carried out with the commercial software “Statistical Package for the Social Sciences” (SPSS for Windows, version 24.0, IBM, USA).

3. Results

3.1. Patients demographic information

A total of 500 ASIA syndrome patients (mean age 43 ± 17 years, median 44 years, range 0–83 years) were recorded in the registry with a female predominance (89%) and 46.6% were smokers. 13.8% had already another prior autoimmune disorder before the exposure to vaccines or foreign materials and 25.8% had a family member with an autoimmune/autoinflammatory disorder. Autoimmune susceptibility, given by either a personal or a familiar history of well-defined autoimmune condition, could be documented for 35.4% of cases. Furthermore, 23.8% reported a history of allergy or an atopic profile (46.2% with drug hypersensitivity, 14.3% with allergy to nickel, 9.2% had asthma, conjunctivitis or rhinitis, 8.4% with food hypersensitivity, 5.0% with skin rash, including urticaria, angioedema, dermatitis, and, finally, 1.7% had allergy to latex; the remaining 15.2% of cases to other allergens, including hay fever, grass, pollen, and pneumo-allergens).

3.2. Well-defined polygenic autoimmune diseases

Among the well-defined immune diseases, the well-defined polygenic autoimmune diseases were the most commonly reported and represented 93% of the reported conditions. Among these, UCTD and Sjögren's syndrome were with the highest prevalence with a percentage of 38.8% and 16.8% among autoimmune diseases, respectively.

Stratifying according to the type of vaccination received, a statistically significant association was found for HBV vaccine (OR 6.72 [95%CI 3.3513.48], $p < 0.0001$) (Table 2).

3.3. Well-defined polygenic autoimmune-inflammatory diseases

The polygenic autoimmune-inflammatory diseases represented 5.8% of the well-defined immune conditions. The most common polygenic autoimmune-inflammatory diseases or with a predominant autoimmune-inflammatory component to be reported in the registry were giant cell arteritis (GCA) (40%) Crohn's disease (30%) and PMR (20%). It's acknowledged that GCA and PMR at the population level exhibit some features pointing towards autoimmune mechanism including MHC-class II associations in GCA but also significant features of innate immunity such as high inflammatory biomarkers, sudden onset of disease, and self-limiting course so strictly speaking they are not pure autoimmune-inflammatory disorders. Patients with polygenic autoimmune-inflammatory diseases had a statistically significant association with influenza vaccination exposure (OR 10.98 [95%CI 3.81–31.67], $p < 0.0001$) (Table 2).

3.4. Mixed pattern diseases (MHC class I associated disease)

Patients with psoriatic arthritis (PsA), ankylosing spondylitis, psoriasis, Behcet's disease or undifferentiated-spondyloarthritis were studied separately as mixed pattern diseases or intermediates between innate and adaptive immunity (Table 2). No significant association was found, either in terms of exposure to vaccines or foreign material.

3.5. Incubation time between adjuvant exposure and immune disease onset stratified by immune disease subtype

No differences could be found in terms of onset time between polygenic autoimmune and autoimmune-inflammatory and mixed pattern diseases (median 1.5 week, 1 week and 1 week, respectively) following vaccination.

3.6. Co-occurrence of different well-defined autoimmune/auto-inflammatory diagnosis

Among the total cases of ASIA syndrome, 5.2% subjects presented > 1 well-defined autoimmune/auto-inflammatory diagnosis. Stratifying according to the type of vaccine administered, a statistically significant association between having more than one well defined immune disease and HBV vaccine (OR 3.15 [95%CI 1.08–9.23], $p = 0.0362$) has been found. Co-occurrences that were reported in our study included primary biliary cholangitis with Sjogren's syndrome, and autoimmune thyroiditis with type I diabetes mellitus.

3.7. Undefined diagnosis of autoimmune/auto-inflammatory disease

Thirty-one percent (31%) of patients had an undefined diagnosis of autoimmune/auto-inflammatory disorder. The common features reported among these subjects were arthralgia (71.0%), chronic fatigue (43.2%) and fever (38.7%). Having an undefined diagnosis was associated with smoking (OR 1.81 [95%CI 1.04–3.15], $p = 0.0361$), but not with exposure to overall vaccines or foreign material. Among these subjects, the overall rate of positivity for autoantibodies was 16.7% which is far lower than the overall positivity in those with well-defined immune disease (55.4%).

3.8. Clinical symptoms of ASIA syndrome cases

Complaints of myalgia were associated with female sex (OR 27.40 [95%CI 1.06–710.72], $p = 0.0463$) and with a positive family history for autoimmune disorders (OR 14.87 [95%CI 1.03–214.48], $p = 0.0475$). With respect to vaccines, myalgia was specifically

Table 1

The prevalence of the various clinical manifestations reported in the ASIA syndrome registry cohort.

Clinical findings	Frequency	Prevalence (%)
Arthralgia	369	73.8%
Chronic fatigue	328	65.6%
Myalgia	254	50.8%
Sleep disturbances	219	43.8%
Fever	194	38.8%
General weakness	247	49.4%
Arthritis	136	27.2%
Neurological manifestations	175	35.0%
Cognitive impairment	172	34.4%
Sicca symptoms	95	19.0%
Raynaud's phenomenon	98	19.6%
Chronic rash	64	12.8%
Lymphadenopathy	141	28.2%
Photosensitivity	55	11.0%
Mouth ulcers	29	5.8%
Postural orthostatic tachycardia syndrome	13	2.6%
Myositis	13	2.6%

associated with exposure to human papilloma virus (HPV) vaccine (OR 85.55 [95%CI 1.65–4426.05], $p = 0.0271$). Pruritus was found to be associated with influenza vaccination (OR 3.90 [95%CI 1.77–8.62]). Further details regarding the reported symptoms among ASIA syndrome patients are reported in Table 1. These symptoms are not specific for certain immune-mediated disorders and thus are not necessarily of an autoimmune nature.

3.9. Laboratory findings among ASIA syndrome cases

Concerning the autoantibody profile status, 54.4% of patients had a positive autoantibody test. Specifically, 48.2% were ANA positive, 7.0% were rheumatoid factor (RF) positive, 6.0% were positive for anti-SSA, 3.8% positive for anti-TPO, 3.4% positive for anti-dsDNA, 2.2% for centromere, 2.0% for anti-Sm, 1.8% for anti-RNP, 1.0% for anti-Scl70 and, finally, 1.0% for anti-SSB. Stratifying for disease subtype, 55.4% of patients with well-defined immune disease and 16.7% of those with undefined autoimmune/auto-inflammatory disease were positive for at least one autoantibody.

3.10. Exposure to adjuvant foreign material in ASIA syndrome cases

The median time between exposure to foreign material and the onset of clinical symptoms was one month and ranged from 2 weeks to 5 years. Identified foreign materials were silicone (in 12.5% of cases), hyaluronic acid (HA) (in 29.2% subjects), Mineral oils (Mo) (in 20.8% individuals) and polyacrylamide (PAM) (in 37.5% of cases). The two most commonly reported polygenic autoimmune diseases after the exposure to a foreign material were UCTD, and Sjogren's disease with a percentage of 19.4% and 2.6%, among the well-defined well-defined immune diseases, respectively. Further details are reported in Table 2.

3.11. Exposure to vaccines in ASIA syndrome cases

The median duration time between exposure to vaccination and onset of symptoms was one week (2 days – 5 years). 48.2% of the population developed clinical symptoms after exposure to at least 1 vaccine (more in detail, 86.7% to 1 vaccine, 10.0% to 2 vaccines, 2.9% to 3 vaccines, and 0.4% to > 3 vaccines). Stratifying according to the type of vaccine administered, 26.4% of the sample developed ASIA syndrome after exposure to hepatitis B virus (HBV) (in detail, 21.9% after the first dose, 24.8% after the second dose, and 53.3% after the third dose). 11.2% of the population developed ASIA syndrome after exposure to influenza vaccine, 10.0% after exposure to HPV vaccination (12.5 after the first dose, 25.0% after the second dose, and 62.5% after

Table 2
Description of the well-defined autoimmune/inflammatory diagnoses.

Well-defined clinical diagnosis	Number of patients	Age	Gender	Exposure to vaccines	Exposure to foreign material
Polygenic autoinflammatory diseases or with a prominent autoinflammatory component					
GCA/PMR	8	67–80 years, 74.5 ± 5.4 years	8 females	Influenza vaccine [8]	–
Giant cell arteritis	4	64–71 years, 66.0 ± 3.4 years	3 females, 1 male	Influenza vaccine [3]	–
Polymyalgia rheumatica	1	27 years	Female	–	Silicone
Adult Still's disease	6	11–48 years, 22.7 ± 14.6 years	4 females, 2 males	HBV [4], influenza vaccine [1], DTP vaccine [1]	–
IBD	1	11	Female	HBV vaccine	–
Crohn's disease	1	35 years	Female	HAV vaccine	–
Ulcerative colitis	3	34–38 years, 36.0 ± 2.0 years	3 males	Influenza vaccine [2], H1N1 vaccine [1]	–
Mixed pattern diseases	1	18 years	Female	HPV vaccine	–
MHC-I-opathies	1	61 years	Female	–	–
Ankylosing spondylitis	1	30 years	Female	DTP vaccine	–
Spondyloarthritis	2	53–54 years, 53.5 ± 0.7 years	2 females	HAV vaccine [1], influenza vaccine [1]	–
Behçet's disease	1	32 years	Female	HBV vaccine	–
Psoriatic arthritis	1	12 years	Female	HPV vaccine	–
Psooriasis	113	15–83 years, 48.5 ± 15.6 years,	101 females, 12 males	HBV vaccine [32], influenza vaccine [30], DTP vaccine [13], Td vaccine [12], smallpox vaccine [7], polio vaccine [5], HAV vaccine [6], HPV vaccine [3], H1N1 vaccine [2], pneumococcal vaccine [1], MMR vaccine [1], yellow fever vaccine [1], measles vaccine [1]	Metal implant (34), tooth amalgam [13], IUD [10], silicone [10], PAL and HA/skin fillers [1]
Polygenic autoimmune diseases	18	14–70 years, 39.7 ± 15.7 years	16 females, 2 males	HBV vaccine [12], MMR vaccine [3], influenza vaccine [3], HPV vaccine [3], TD vaccine [2], DTD vaccine [1], DTP [1], oral typhoid vaccine [1], HAV vaccine [1], JE vaccine [1]	Mo [2], silicone [1]
Vasculitides	49	25–72 years, 46.6 ± 12.0 years	48 females, 1 male	DTP vaccine [7], HBV vaccine [6], HPV vaccine [3], oral typhoid vaccine [1], HAV vaccine [1], MMR vaccine [1], JE vaccine [1], influenza vaccine [1]	HA [3], silicone [2], PAC [2], PAL [1], Mo [1]
ANCA-associated vasculitis	10	16–47 years, 29.7 ± 9.9 years	10 females	HBV vaccine [9], HPV vaccine [1]	–
Polyarteritis nodosa	5	31–55 years, 44.8 ± 11.4 years	5 females	HBV vaccine [2]	Silicone [2], PAC [1], metal implant [1], skin filler [1], IUD [1]
HS purpura	2	6 years	1 female, 1 male	HBV vaccine [2]	–
RA, SLE and CTD	1	39 years	Female	DTP vaccine	–
UCTD	2	40–57 years, 48.5 ± 12.0 years	2 females	HBV vaccine	Silicone
Systemic lupus erythematosus	4	33–45 years, 40.8 ± 5.3 years	3 females, 1 male	HBV vaccine [3], influenza vaccine [1], HAV vaccine [1]	–
Sjogren's syndrome	20	15–55 years, 31.2 ± 8.9 years	18 females, 2 males	HBV vaccine [18], HPV vaccine [2]	–
RA	13	4–69 years, 17.8 ± 17.7 years	7 males, 6 females	HBV vaccine [11], HPV vaccine [2]	–
Systemic sclerosis/morphea	8	11–66 years, 36.4 ± 24.2 years	6 females, 2 males	HBV vaccine [4], influenza vaccine [2], HAV vaccine [1], DTP vaccine [1], HPV vaccine [13]	–
Dermatomyositis	15	12–64 years, 45.1 ± 16.9 years	14 females, 1 male	HPV vaccine [6]	–
Recurrent polyorchondritis	6	12–22 years, 16.8 ± 3.8 years	6 females	HPV vaccine [6]	–
APS					
MCTD					
Organ specific					
Multiple sclerosis/optic neuritis/neuromyelitis optica	20				
Diabetes mellitus type 1	13				
GBS	8				
Dysautonomic neuropathy	15				
POTS	6				

(continued on next page)

Table 2 (continued)

Well-defined clinical diagnosis	Number of patients	Age	Gender	Exposure to vaccines	Exposure to foreign material
Autoimmune liver diseases	6	11–39 years, 25.2 ± 10.8 years	5 females, 1 male	HBV [6], influenza vaccine [1], MMR vaccine [1]	–
Transverse myelitis	4	14–67 years, 33.0 ± 23.7 years	3 females, 1 male	HAV vaccine [1], HBV vaccine [3], DPT vaccine [1], HPV vaccine [1], MCV4 vaccine [1]	–
Autoimmune encephalitis	2	17–37 years, 27.0 ± 14.1 years	2 males	HBV vaccine [2]	–
Hemolytic anemia	1	14 years	Male	HBV vaccine	–
Autoimmune thyroiditis	2	14–40 years, 27.0 ± 18.4 years	2 females	HPV vaccine [1]	–
Adrenal insufficiency	1	9 years	Female	HBV vaccine	–
Inflammatory polyradiculopathy	1	53 years	Male	Influenza vaccine	–
PBC	2	52–56 years, 54.0 ± 2.8 years	2 females	–	PAC and HA [1], PAL [1]
CIDP	1	52 years	Female	HBV vaccine	–
Celiac disease	1	7 years	Male	DTP vaccine, HBV vaccine	–
Others autoimmune/rheumatic diseases					
Sarcoidosis	4	35–53 years, 45.8 ± 7.9 years	3 females, 1 male	DTP vaccine [1], HBV vaccine [1]	PLA [1], HAM [1], HA [1]
Panniculitis	2	32–39 years	2 females	HPV vaccine [1]	–
Alopecia	1	11 years	Female	HBV vaccine	–
Macrophagic myofasciitis	1	13 years	Female	HPV vaccine	–
Inflammatory polyarthritis	1	62 years	Female	HBV vaccine	–
Autoimmune recurrent abortions	2	32–39 years, 35.5 ± 4.9 years	2 females	–	–
Juvenile RA	2	4–15 years, 9.5 ± 7.8 years	1 female, 1 male	HBV vaccine [2]	–
Fibromyalgia	36	11–66 years, 28.0 ± 14.2 years	34 females, 2 males	HPV vaccine [1,6], HBV vaccine [1,4], influenza vaccine [1], HAV vaccine [1]	Silicone [6]
CFS	11	12–54 years, 29.7 ± 17.9 years	7 females, 4 males	HBV vaccine [8], HPV vaccine [2], DTd vaccine [1], intranasal influenza vaccine [1], HAV vaccine [1], oral typhoid vaccine [1], JE vaccine [1]	Silicone [1]

APS: anti-phospholipid syndrome, CFS: chronic fatigue syndrome, CIDP: chronic inflammatory demyelinating polyneuropathy, CTD: connective tissue disease, DTP: diphtheria/tetanus/pertussis, GBS: Guillain-Barré syndrome, GCA: giant cell arteritis, HA: hyaluronic acid, HAV: hepatitis A virus, HBV: hepatitis B virus, HPV: human papilloma virus, IBD: inflammatory bowel disease, IUD: intrauterine device, JE: Japanese encephalitis, MCTD: mixed connective tissue disease, MCV4: meningococcal conjugate vaccine 4, MMR: mumps/mumps/rubella, Mo: mineral oil, PAC: polyacrylamide gel, PAL: polyalkylamide gel, PBC: primary biliary cholangitis, POTS: postural orthostatic tachycardia syndrome, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, UCTD: undifferentiated connective tissue disease.

the third dose), and 8.4% after exposure to diphtheria-tetanus-pertussis (DTP) immunisation. With lower rates, 2.6% of cases developed after exposure to measles, mumps, and rubella (MMR) immunisation, 2.0% after exposure to hepatitis A virus (HAV) vaccine (in detail, 80.0% after the first dose, and 20.0% after the second dose), 0.8% after exposure to H1N1 influenza vaccine and, finally, 0.4% after exposure to pneumococcal vaccine.

3.12. Pharmacological treatment

Among the overall ASIA syndrome patients, 2.4% and 10.2% were treated with biologics and disease-modifying antirheumatic drugs (DMARDs), respectively, whereas 13.6% hydroxychloroquine and 34.0% prednisone or other glucocorticoids.

3.13. Comparison between the two registry studies (2011–2016 January vs 2016 February–2019 February)

Comparing the ASIA syndrome cases inserted between 2011 and 2016 January (previously published paper [16]) to those from 2016 February–2019 February, the rate of the classic symptoms (arthralgia chronic fatigue, myalgia, sleep disturbances, general weakness, neurological manifestations, cognitive impairment) of ASIA has increased, with few exceptions (arthritis, chronic rash, mouth ulcers and postural orthostatic tachycardia syndrome (POTS), which tended to decrease, and photosensitivity, which remained stable) (Table 3).

Tables 4 shows the changes in terms of rate in well-defined immune clinical diagnosis between our previously published paper and the current update. More in detail, well-defined immune diagnoses tended to decrease, with few exceptions (PsA, psoriasis and undifferentiated-spondyloarthritis, connective tissue diseases (CTDs) such as Sjogren's syndrome, antiphospholipid syndrome (APS) and mixed connective tissue disease (MCTD), organ-specific disorders including dysautonomic neuropathy and autoimmune thyroiditis, primary biliary cholangitis (PBC) and celiac disease, panniculitis, alopecia, inflammatory polyarthritis and autoimmune recurrent abortions).

4. Discussion

The mechanistic explanation behind the development of an autoimmune/autoinflammation disease is extremely complex and thought to be a result of a complex interplay of several factors, especially environmental and genetic ones [17,18]. To prove a cause-effect link between a compound and a clinical disorder is one of the hardest and complicated issues in medicine and normally requires at least two

elements: reproducible statistically significant association and plausible underlying mechanisms.

Some scholars claim that the link between vaccine administration or exposure to foreign material and the insurgence of autoimmune/inflammatory and immune mediated events is only alleged, and constitutes a prejudice and a “false myth” that reduces/deters vaccination coverage [4]. However, despite being rare, this link is real [7]. Vaccine adverse events, indeed, rarely occur and to be properly captured require large epidemiological surveys (such as cohort studies) or meta-analytical network investigations, which are sufficiently statistically powered to detect such relations. Nevertheless, a significant link between influenza immunisation and Guillain-Barré syndrome has been reported [19]. Also the exposure to MMR vaccine has been associated with immune thrombocytopenic purpura onset [20]. A link between yellow fever immunisation and the insurgence of viscerotropic and neurotropic diseases, oral vaccination against poliovirus or exposure to smallpox vaccine and the occurrence of neurological complications was also reported [21–23]. Given that other side-effects occurred after vaccination, there is the need of evidence-based studies. Due to the dearth of information and robust data, ASIA syndrome is an adequate umbrella term to gather together events and reactions apparently unrelated, which share exposure to vaccines, silicone or other foreign material as a common root [9]. However, we would like to stress that these clinical phenomena have an extremely low occurrence rate. Immunisation practices offer many clinical benefits, having contributed to the eradication and control of several communicable diseases and thus improving and enhancing the human quality of life [7].

Wang et al. [24] have recently performed a meta-analysis pooling 16 observational studies, finding a significantly increased risk of SLE (RR = 1.50 [95%CI 1.05–2.12], $p = 0.02$) and an increased risk of RA (RR = 1.32 [95%CI 1.09–1.60], $p = 0.004$) following immunisation. The relative risk (RR) remained elevated and significant, also after reducing the time between vaccine administration and the insurgence of autoimmune disorder.

Adjuvants can interact with different components of the immune system including both innate and adaptive immunity [25,26]. To facilitate the comprehension of such complex link between vaccine-adjuvants and immune-mediated events, a classification has been proposed by Koenig and co-authors [27]. Classical adaptive immune diseases induced by (dysregulation mainly of B and T cells) are at one end of the spectrum and pure innate diseases (dysregulation of the innate immune cells or due to permeability barrier defects, excessive tissue repair process, and remodelling responses) are on the other side [14]. Thus, adjuvants that activate innate immune components such as myeloid cells, neutrophils, Toll-like receptors (TLRs), and the

Table 3
Changes in clinical symptoms of ASIA syndrome frequency and percentage between our previously published paper and the current update.

Clinical findings	Overall frequency and percentage (01/2016–02/2019 – present paper)	Frequency and percentage (2011–01/2016 – previous paper)	Frequency and percentage (02/2016–2019 – present update)	Change
Arthralgia	369 (73.8%)	184 (61.3%)	185 (92.5%)	↑
Chronic fatigue	328 (65.6%)	178 (59.3%)	150 (75.0%)	↑
Myalgia	254 (50.8%)	147 (49.0%)	107 (53.5%)	↑
Sleep disturbances	219 (43.8%)	112 (37.3%)	107 (53.5%)	↑
Fever	194 (38.8%)	101 (33.7%)	93 (46.5%)	↑
General weakness	247 (49.4%)	100 (33.3%)	147 (73.5%)	↑
Arthritis	136 (27.2%)	88 (29.3%)	48 (24.0%)	↓
Neurological manifestations	175 (35.0%)	78 (26.0%)	97 (48.5%)	↑
Cognitive impairment	172 (34.4%)	63 (21.0%)	109 (54.5%)	↑
Sicca symptoms	95 (19.0%)	55 (18.3%)	40 (20.0%)	↑
Raynaud's phenomenon	98 (19.6%)	48 (16.0%)	50 (25.0%)	↑
Chronic rash	64 (12.8%)	47 (15.7%)	17 (8.5%)	↓
Lymphadenopathy	141 (28.2%)	43 (14.3%)	98 (49.0%)	↑
Photosensitivity	55 (11.0%)	33 (11.0%)	22 (11.0%)	↔
Mouth ulcers	29 (5.8%)	18 (6.0%)	11 (5.5%)	↓
POTS	13 (2.6%)	13 (4.3%)	0 (0.0%)	↓
Myositis	13 (2.6%)	7 (2.3%)	6 (3.0%)	↑

Table 4
Changes in well-defined clinical diagnosis between our previously published paper and the current update.

Well-defined clinical diagnosis	Total number of patients	Number of patients (2011–01/2016 – previous paper)	Number of patients (02/2016–2019 – update)	Change
Polygenic autoinflammatory diseases or with a prominent autoinflammatory component				
GCA/PMR	12 (2.4%)	11 (3.7%)	1 (0.5%)	↓
Adult Still's disease	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
IBD	7 (1.4%)	6 (2.0%)	1 (0.5%)	↓
Mixed pattern diseases				
MHC-I-opathies	7 (1.4%)	2 (0.7%)	5 (2.5%)	↑
Ankylosing spondylitis	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Psoriasis	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Behçet's disease	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Psoriatic arthritis	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Undifferentiated-SpA	3 (0.6%)	0 (0.0%)	3 (1.5%)	↑
Polygenic autoimmune diseases				
Vasculitides	4 (0.8%)	4 (1.3%)	0 (0.0%)	↓
ANCA-associated vasculitis	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓
Polyarteritis nodosa	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
HS purpura	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
RA, SLE and CTD	204 (40.8%)	127 (42.3%)	77 (25.7%)	↓
UCTD	113 (22.6%)	78 (26.0%)	35 (17.5%)	↓
SLE	18 (3.6%)	18 (6.0%)	0 (0.0%)	↓
Sjögren's syndrome	49 (9.8%)	11 (3.7%)	38 (19.0%)	↑
RA	10 (2.0%)	10 (3.3%)	0 (0.0%)	↓
Systemic sclerosis/morphea	5 (1.0%)	5 (1.7%)	0 (0.0%)	↓
Dermatomyositis	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓
Recurrent chondrodysplasia	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
APS	2 (0.4%)	1 (0.3%)	1 (0.5%)	↑
MCTD	4 (0.8%)	1 (0.3%)	3 (1.5%)	↑
Organ specific	83 (16.6%)	70 (23.3%)	13 (6.5%)	↓
Multiple sclerosis/optic neuritis/neuromyelitis optica	20 (4.0%)	20 (6.7%)	0 (0.0%)	↓
Diabetes mellitus type 1	13 (2.6%)	12 (4.0%)	1 (0.5%)	↓
GBS	8 (1.6%)	8 (2.7%)	0 (0.0%)	↓
Dysautonomic neuropathy	15 (3.0%)	7 (2.3%)	8 (4.0%)	↑
POTS	6 (1.2%)	6 (2.0%)	0 (0.0%)	↓
Autoimmune liver diseases	6 (1.2%)	5 (1.7%)	1 (0.5%)	↓
Transverse myelitis	4 (0.8%)	4 (1.3%)	0 (0.0%)	↓
Autoimmune encephalitis	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓
Haemolytic anemia	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Autoimmune thyroiditis	2 (0.4%)	1 (0.3%)	1 (0.5%)	↑
Adrenal insufficiency	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Inflammatory polyradiculopathy	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
PBC	2 (0.4%)	1 (0.3%)	1 (0.5%)	↑
CIDP	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Celiac disease	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Other autoimmune/rheumatic diseases	60 (12.0%)	53 (17.7%)	7 (3.5%)	↓
Fibromyalgia	36 (7.2%)	36 (12.0%)	0 (0.0%)	↓
CFS	11 (2.2%)	11 (3.7%)	0 (0.0%)	↓
Sarcoidosis	4 (0.8%)	3 (1.0%)	1 (0.5%)	↓
Panniculitis	2 (0.4%)	0 (0.0%)	2 (1.0%)	↑
Alopecia	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Macrophagic myofasciitis	1 (0.2%)	1 (0.3%)	0 (0.0%)	↓
Inflammatory polyarthritis	1 (0.2%)	0 (0.0%)	1 (0.5%)	↑
Autoimmune recurrent abortions	2 (0.4%)	0 (0.0%)	2 (1.0%)	↑
Juvenile RA	2 (0.4%)	2 (0.7%)	0 (0.0%)	↓

GCA: giant cells arteritis, PMR: polymyalgia rheumatica, IBD: inflammatory bowel disease, SpA: spondyloarthritis, HS purpura: henoch schonlein purpura,

RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, CTD: connective tissue disease, UCTD: undifferentiated connective tissue disease, APS: anti-phospholipid syndrome, MCTD: mixed connective disease, GBS: guillain-barré syndrome, POTS: postural orthostatic tachycardia syndrome, PBC: primary biliary cholangitis, CIDP: chronic inflammatory demyelinating polyneuropathy, CFS: chronic fatigue syndrome.

inflammasome are expected to induce predominantly innate immune disorders and therefore lead to the development of autoinflammatory phenotype of adjuvant mediated disorders. In contrast, compounds that activate predominately adaptive immune mechanisms such as antigen presentation, antibody production, B cells, and T cells are more often linked with autoimmune conditions. In our study, well-defined polygenic autoimmune diseases were reported to be induced more frequently following exposure to HBV vaccine, whereas polygenic auto-inflammatory disorders were more often reported after exposure to influenza vaccination. Of note, several vaccines include different adjuvants, yet the exact the exact mechanism of action of the different adjuvants is yet to be defined.

According to our study, different vaccine-adjuvants were able to induce either autoimmune or autoinflammation disorders, although with predilection for certain self-inflammation subtype. Nevertheless, our data strongly suggest that autoimmune diseases are far more common than autoinflammatory diseases after the exposure to vaccine adjuvants. In the past, macrophagic myofasciitis (MMF) and gulf war syndrome were more frequently reported than the present day. Whether this is related to change of adjuvant types or other factors is yet to be clarified.

Concerning exposure to foreign material, silicone are polymers that are commonly used in various medical applications [6]. These compounds significantly elicit immune system activation and responses, leading to tissue alterations and injuries. Different studies have shown that silicone breast implants (SBIs) may be associated to fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth [28–30]. A robust proof of this is given by the fact that removing SBIs leads to amelioration of the symptoms [31]. In addition, we have recently performed a nation-wide cross-sectional study including > 24 thousand women with SBIs and > 98 thousand matched with SBIs to assess the link between SBIs and autoimmunity [6]. The adjusted risk of being diagnosed with an autoimmune/rheumatic disorder was computed to be 1.22 [95%CI 1.18–1.26]. The most prominent associations with SBIs (OR > 1.5, $p < 0.001$) were found with Sjögren's syndrome (OR 1.58), systemic sclerosis (SSc; OR 1.63) and sarcoidosis (OR 1.98).

The international ASIA registry contributes to the advancement of vaccine- and foreign material-related knowledge in terms of their safety profile and potential adverse events, updating and expanding our previously published report. Furthermore, it shows that the vast majority of the well-defined immune diseases to be reported are of autoimmune nature rather than autoinflammation or intermediate immune diseases. Further studies, including well-conducted, high quality large epidemiological surveys and randomized trials, are needed to confirm and replicate our findings.

In conclusion, it is extremely important to highlight that the main objective of the current study is not to discourage vaccinations, which are crucial against certain infections. Our findings show that potential adjuvant associated immune mediated disorders are predominantly autoimmune in nature rather than innate or autoinflammatory in nature. Immune conditions following vaccination are relatively rare, but should not be underestimated and thus the production of better compounds acting as adjuvants with a better efficacy and safety profile should be promoted. Nowadays and according to the literature, the benefits of vaccinations far outweigh the risk of immune side effects.

Ethics approval and consent to participate

Due to anonymous archival data, not consent form was required.

Consent to publish

All authors reviewed the manuscript and consented its publishing.

Competing interest

YS appears in the Special vaccine compensation court in Washington US. The Rest of the authors do not declare any conflict of interest.

Competing financial interests

The authors declare no competing financial interests. This work is supported by the grant of the Government of the Russian Federation for the state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

Availability of data and materials

Data was obtained from the international ASIA syndrome registry.

Author contributions

A.W., N.L.B. and Y.S. designed the study and wrote the manuscript. A.W., N.L.B., M.A., J.A.R., E.E.V, C.B. and MyQ collected and analysed the data. A.W., M.A., D.M., G.D. and H.A., and Y.S. mainly interpreted the results. A.W., N.L.B., D.M., C.B., G.D., H.A. and Y.S. added critical discussions on analyses and results. All authors reviewed the manuscript.

Acknowledgement

Not applicable.

References

- [1] Y. Shoenfeld, N. Agmon-Levin, 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants, *J. Autoimmun.* 36 (2011) 4–8.
- [2] N.L. Bragazzi, A. Watad, K. Sharif, M. Adawi, G. Aljadeff, H. Amital, Y. Shoenfeld, Advances in our understanding of immunisation and vaccines for patients with systemic lupus erythematosus, *Expert. Rev. Clin. Immunol.* 13 (2017) 939–949.
- [3] O. Vera-Lastra, G. Medina, M.D.P. Cruz-Dominguez, L.J. Jara, Y. Shoenfeld, Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum, *Expert. Rev. Clin. Immunol.* 9 (2013) 361–373.
- [4] O. Vera-Lastra, G. Medina, M.D.P. Cruz-Dominguez, P. Ramirez, J.A. Gayosso-Rivera, H. Anduaga-Dominguez, C. Lievana-Torres, L.J. Jara, Human adjuvant disease induced by foreign substances: a new model of ASIA (Shoenfeld's syndrome), *Lupus* 21 (2012) 128–135.
- [5] O. Vera-Lastra, G. Medina, M.D.P. Cruz-Dominguez, G.M. Ramirez, R.B.P. Blancas, A.L.P. Amaro, A.V. Martinez, J.S. Delgado, L.J. Jara, Autoimmune/inflammatory syndrome induced by mineral oil: a health problem, *Clin. Rheumatol.* 37 (2018) 1441–1448.
- [6] A. Watad, V. Rosenberg, S. Tiosano, J.W. Cohen Tervaert, Y. Yavne, Y. Shoenfeld, V. Shalev, G. Chodick, H. Amital, Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis, *Int. J. Epidemiol.* 47 (2018) 1846–1854.
- [7] N.L. Bragazzi, A. Watad, H. Amital, Y. Shoenfeld, Debate on vaccines and autoimmunity: do not attack the author, yet discuss it methodologically, *Vaccine* 35 (2017) 5522–5526.
- [8] Y. Segal, S. Dahan, K. Sharif, N.L. Bragazzi, A. Watad, H. Amital, The value of Autoimmune Syndrome Induced by Adjuvant (ASIA) - shedding light on orphan diseases in autoimmunity, *Autoimmun. Rev.* 17 (2018) 440–448.
- [9] A. Watad, M. Quresma, S. Brown, J.W. Cohen Tervaert, I. Rodriguez-Pint, R. Cervera, C. Perricone, Y. Shoenfeld, Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) - an update, *Lupus* 26 (2017) 675–681.
- [10] L.J. Jara, G. Garcia-Collinot, G. Medina, M.D.P. Cruz-Dominguez, O. Vera-Lastra, R.A. Carranza-Muleiro, M.A. Saavedra, Severe manifestations of autoimmune syndrome induced by adjuvants (Shoenfeld's syndrome), *Immunol. Res.* 65 (2017) 8–16.
- [11] A. Watad, P. David, S. Brown, Y. Shoenfeld, Autoimmune/inflammatory syndrome induced by adjuvants and thyroid autoimmunity, *Front. Endocrinol. (Lausanne)* 24 (2017) 150.
- [12] A. Watad, S. Azrielant, N.L. Bragazzi, K. Sharif, P. David, I. Katz, G. Aljadeff, M. Quresma, G. Tanay, M. Adawi, H. Amital, Y. Shoenfeld, Seasonality and autoimmune diseases: the contribution of the four seasons to the mosaic of autoimmunity, *J. Autoimmun.* 82 (2017) 13–30.
- [13] S. Colafrancesco, N. Agmon-Levin, C. Perricone, Y. Shoenfeld, Unraveling the soul of autoimmune diseases: pathogenesis, diagnosis and treatment adding dowels to the puzzle, *Immunol. Res.* 56 (2013) 200–205.
- [14] D. McGonagle, M.F. McDermott, A proposed classification of the immunological diseases, *PLoS Med.* 3 (2006) e297.
- [15] M.T. Arango, C. Perricone, S. Kivity, E. Cipriano, F. Ceccarelli, G. Valesini, Y. Shoenfeld, HLA-DRB1 the notorious gene in the mosaic of autoimmunity, *Immunol. Res.* 65 (2017) 82–98.
- [16] A. Watad, M. Quresma, N.L. Bragazzi, R. Cervera, J.W.C. Tervaert, H. Amital, Y. Shoenfeld, The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry, *Clin. Rheumatol.* 37 (2018) 483–493.
- [17] C.C. Goodnow, Multistep pathogenesis of autoimmune disease, *Cell* 130 (2007) 25–35.
- [18] G. Aljadeff, E. Longhi, Y. Shoenfeld, Bisphenol A: a notorious player in the mosaic of autoimmunity, *Autoimmunity* 51 (2018) 370–377.
- [19] D.A. Salmon, M. Proschan, R. Forshee, P. Gargiullo, W. Bleser, D.R. Burwen, F. Cunningham, P. Garman, S.K. Greene, G.M. Lee, C. Vellozzi, W.K. Yih, B. Gellin, N. Lurie, H1N1 GBS Meta-Analysis Working Group, Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis, *Lancet.* 381 (2013) 1461–1468.
- [20] V. Cecinati, N. Principi, L. Brescia, P. Giordano, S. Esposito, Vaccine administration and the development of immune thrombocytopenic purpura in children, *Hum. Vaccine Immunother.* 9 (2013) 1158–1162.
- [21] D.A. Geier, M.R. Geier, Quadrivalent human papillomavirus vaccine and autoimmune adverse events: a case-control assessment of the vaccine adverse event reporting system (VAERS) database, *Immunol. Res.* 65 (2017) 46–54.
- [22] A. Miravalle, J. Biller, E. Schnitzler, A. Bonwit, Neurological complications following vaccinations, *Neurol. Res.* 32 (2010) 285–292.
- [23] D.A. Geier, M.R. Geier, A case-control study of serious autoimmune adverse events following hepatitis B immunisation, *Autoimmunity* 38 (2005) 295–301.
- [24] B. Wang, X. Shao, D. Wang, D. Xu, J.A. Zhang, Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: a systematic review and meta-analysis, *Autoimmun. Rev.* 16 (2017) 756–765.
- [25] S. Awate, L.A. Babuik, G. Mutwiri, Mechanisms of action of adjuvants, *Front. Immunol.* 4 (2013) 114.
- [26] D.J. Marciani, Vaccine adjuvants: role and mechanisms of action in vaccine immunogenicity, *Drug Discov. Today* 8 (2003) 934–943.
- [27] H.C. Koenig, A. Sutherland, H.S. Izurieta, D. McGonagle, Application of the immunological disease continuum to study autoimmune and other inflammatory events after vaccination, *Vaccine* 29 (2011) 913–919.
- [28] J.W. Cohen Tervaert, Autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome): a new flame, *Autoimmun. Rev.* 17 (2018) 1259–1264.
- [29] J.W. Cohen Tervaert, M.J. Colaris, R.R. van der Hulst, Silicone breast implants and autoimmune rheumatic diseases: myth or reality, *Curr. Opin. Rheumatol.* 29 (2017) 348–354.
- [30] J.W. Cohen Tervaert, R.M. Kappel, Silicone implant incompatibility syndrome (SIIS): a frequent cause of ASIA (Shoenfeld's syndrome), *Immunol. Res.* 56 (2013) 293–298.
- [31] M. de Boer, M. Colaris, R.R.W.J. van der Hulst, J.W. Cohen Tervaert, Is explantation of silicone breast implants useful in patients with complaints? *Immunol. Res.* 65 (2017) 25–36.
- [32] D. McGonagle, S.Z. Aydin, A. Gül, A. Mahr, H. Direskeneli, 'MHC-I-opathy'-unified concept for spondyloarthritis and Behçet disease, *Nat. Rev. Rheumatol.* 11 (12) (2015 Dec) 731–740.