Summary of Studies Featured in VACCINES & AUTOIMMUNITY

Edited by Yehuda Shoenfeld, Nancy Agmon-Levin and Lucija Tomljenovic

This eBook contains the conclusions of studies by leading researchers from 14 countries on the role of adjuvants in vaccines and how they can induce diverse autoimmune clinical manifestations in genetically prone individuals.

WILEY Blackwell Copyright © 2015
# TABLE OF CONTENTS

## PART 1  Mosaic of Autoimmunity

1. Role of Adjuvants in Infection and Autoimmunity
2. Infections as Adjuvants for Autoimmunity: The Adjuvant Effect
3. Experimental Models of Adjuvants
4. Answers to Common Misconceptions Regarding the Toxicity of Aluminum Adjuvants in Vaccines
5. Allergy and Autoimmunity Caused by Metals: A Unifying Concept
6. Genetics and Vaccinology
7. Silicone and Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)
8. Silicone Breast Implants and Autoimmune/Inflammatory Syndrome induced by Adjuvants (ASIA): A Literature Search
9. Autoantibodies Induced by Vaccine
10. The ASIA Syndrome Registry
11. Vaccination in Autoimmune Diseases
12. Vaccination in Patients with Autoimmune Inflammatory Rheumatic Diseases

## PART 2  Studies on Autoimmune Conditions Induced by Vaccination

13. Measles, Mumps, and Rubella Vaccine: A Triad to Autoimmunity
14. Yellow Fever Vaccine and Autoimmunity
15. Antiphospholipid Syndrome and Vaccines
16. Hepatitis B Vaccination and Autoimmunity
17. Adverse Reactions to Human Papillomavirus Vaccines
18. Influenza Vaccine and Autoimmune Diseases
19. Vaccines and Autoimmunity: Meningococcal Vaccines
20. Pneumococcal Vaccines and Autoimmune Phenomena
21. BCG and Autoimmunity
### PART 3 Autoimmune Diseases Solicited by Vaccination

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Systemic Lupus Erythematosus Induced by Vaccines</td>
<td>16</td>
</tr>
<tr>
<td>23</td>
<td>Vasculitides</td>
<td>17</td>
</tr>
<tr>
<td>24</td>
<td>Vaccinations in Rheumatoid Arthritis</td>
<td>18</td>
</tr>
<tr>
<td>25</td>
<td>Undifferentiated Connective-Tissue Diseases</td>
<td>19</td>
</tr>
<tr>
<td>26</td>
<td>Vaccines, Infections, and Alopecia Areata</td>
<td>20</td>
</tr>
<tr>
<td>27</td>
<td>Aluminum Particle Biopersistence Systemic Transport, and Long-Term Safety: Macrophagic Myositis and Beyond</td>
<td>20</td>
</tr>
<tr>
<td>28</td>
<td>Immune Thrombocytopenic Purpura: Between Infections and Vaccinations</td>
<td>21</td>
</tr>
<tr>
<td>29</td>
<td>Vaccinations and Type 1 Diabetes</td>
<td>22</td>
</tr>
<tr>
<td>30</td>
<td>Narcolepsy and H1N1 Vaccine</td>
<td>22</td>
</tr>
<tr>
<td>31</td>
<td>Non-nutritional Environmental Factors Associated with Celiac Disease: Infections and Vaccinations</td>
<td>23</td>
</tr>
<tr>
<td>32</td>
<td>Polymyalgia Rheumatica</td>
<td>24</td>
</tr>
<tr>
<td>33</td>
<td>Acute Disseminated Encephalomyelitis: Idiopathic, Post-infectious, and Post-vaccination</td>
<td>24</td>
</tr>
<tr>
<td>34</td>
<td>Fibromyalgia, Chronic Fatigue, Functional Disorders, and Vaccination: Where Do We Stand?</td>
<td>25</td>
</tr>
<tr>
<td>35</td>
<td>Bullous Dermatoses, Infectious Agents, and Vaccines</td>
<td>25</td>
</tr>
<tr>
<td>36</td>
<td>Infectious, Vaccinations, and Chronic Fatigue Syndrome</td>
<td>26</td>
</tr>
<tr>
<td>37</td>
<td>Myositis and Vaccines</td>
<td>26</td>
</tr>
</tbody>
</table>
Due to the adverse effects exerted by adjuvants there is no controversy over the need for safer adjuvants for incorporation into future vaccines. The problem with the pure recombinant or synthetic antigens used in the modern-day vaccines is that they are generally far less immunogenic than older-style live or killed whole-organism vaccines. This has created a major need for improved and more powerful adjuvants for use in these vaccines (Petrovsky and Aguilar, 2004). With few exceptions, alum remains the major adjuvant approved for human use in the majority of countries worldwide. Although alum is able to induce a good antibody (Th2) response, it has little capacity to stimulate cellular (Th1) immune responses, which are so important for protection against many pathogens. In addition, alum has the potential to cause severe local and systemic side effects, including sterile abscesses, eosinophilia, and myofascitis, although, fortunately, most of the more serious side effects are relatively rare. Consequently, there is a major unmet need for safer and more effective adjuvants suitable for human use. In particular, there is demand for safe and nontoxic adjuvants capable of stimulating cellular (Th1) immunity. Several other adjuvants besides alum have been approved to date for use in human vaccines, among them MF59 in some viral vaccines, MPL, AS04, As01B and AS02A against viral and parasitic infections, virosomes for HBV, HPV, and HAV, and cholera toxin for cholera (Table 1.3) (Reed et al., 2009).

Other needs in light of new vaccine technologies or adjuvants suitable for use with mucosally delivered vaccines, DNA vaccines, cancer, and autoimmunity vaccines. Each of these areas is highly specialized, with its own unique needs with respect to suitable adjuvant technology. Although controversial, the high sensitivity of TLR for microbial ligands is what makes adjuvants that mimic TLR ligands such a prime candidate for enhancing the overall effects of antigen-specific vaccinations on immunological memory. The expression of TLRs is vast, as they are found on the cell membranes of innate immune cells (DCs macrophages, natural killer cells), cells of the adaptive immunity (T and B lymphocytes), and nonimmune cells (epithelial cells). This further substantiates the importance of administering vaccines with adjuvants in the form of TLR ligands, as they will be capable of eliciting their positive effects across the entire spectrum of innate and adaptive immunity. Nevertheless, there are certainly adjuvants whose immune stimulatory function completely bypasses the putative requisite for TLR signaling (Table 1.4). In short, all TLR ligands are adjuvants but not all adjuvants are TLR ligands. We can conclude that there are, in all likelihood, other receptors besides TLRs that have not yet been characterized, opening a field of future research. Perhaps future adjuvants occupying these putative receptors will be employed to bypass the TLR signaling pathway completely, in order to circumvent common side effects of adjuvant-activated TLRs, such as a local inflammation in the general malaise felt because of the costly whole-body immune response to antigen. Such issue will be the subject of much debate for future researchers.
Conclusions

Empirical formulations of adjuvants and breakthrough immunological theories in the 20th century have played important roles in advancing our understanding of the immune system. Adjuvant and natural infections can exert potent immunostimulatory activities through the adjuvant effect, which can lead to autoimmune disease. The powerful adjuvant effect cannot be utilized to develop novel antitumor therapies and effective vaccines. The goal of the vaccine is to reproduce the protection afforded by an infection, while minimizing the risks. Recent advances in the understanding of the molecular mechanisms involved in immune cell activation have provided an opportunity to fine-tune and vaccine development and the adjuvant effect for the strategic activation of specific immune pattern recognition receptors.

Conclusions

Several kinds of animal models have been employed to investigate adjuvant effects and midterm reactions in vivo, in an attempt to better unravel adverse events in humans following vaccinations or prosthesis implantations. Higher organisms, such as primates are rarely used; rather, different mouse models have provided the bulk of the evidence for vaccine and adjuvants effects in living beings. Interestingly, adverse reactions rarely take place in non-overtly autoimmune-prone models, acting as putative triggering agents on an apparent neutral background; further, spontaneous autoimmune-prone strains are rapidly doomed to autoimmunity as they
undergo adjuvant administration. Notably, animal models rendered transgenic for non-autoimmune-related alteration (e.g. mutation of V factor Leiden) show a greater susceptibility in developing an acquired autoimmune condition following adjuvant administration (e.g. antiphospholipid syndrome) suggesting that genetic alterations, though devoid of immune influence, may result in autoimmunity as soon as a triggering agent is encountered. The underlying mechanisms are still unknown, but a role for perturbations in the cytokine production via Toll-like receptor (TLR) stimulation is likely, alongside the capability of adjuvants to foster an immune response, whether protective or aberrant. Further studies are warranted, in order to progressively unravel the pathogenic pathways elicited by adjuvants and to definitely state the caution required in treating autoimmunity-bearing patients.

**Answers to Common Misconceptions Regarding the Toxicity of Aluminum Adjuvants in Vaccines**

**CHAPTER 4**

**Lucija Tomljenovic**  
Neural Dynamics Research Group  
University of British Columbia  
Vancouver, BC, Canada

**Christopher A. Shaw**  
Department of Ophthalmology and Visual Sciences  
Programs in Experimental Medicine and Neuroscience  
University of British Columbia  
Vancouver, BC, Canada

**Conclusions**

Al salts are the most widely used adjuvants today, and have been since the 1920s (Glenny et al., 1926). The fact that they can trigger pathological immunological responses and cascade of unwanted health effects has been relatively underappreciated to date. The risks associated with vaccine-derived derived Al threefold: it can persist in the body, it can trigger pathological immunological responses, and it can make its way into the CNS, where it can drive deleterious immunoinflammatory and excitotoxic processes. Because infants and children may be most at risk for complications following vaccination, a more rigorous evaluation of potential vaccine-related adverse health impacts in pediatric populations is urgently needed. The recognition of ASIA as a vaccine adjuvant-triggered pathology should alert and encourage both physicians and patients to report vaccine adverse conditions, in order to enable a better estimation of the true prevalence of ASIA. It is clear that the role of adjuvants in the pathogenesis of immune-mediated diseases can no longer be ignored, especially in view of the fact that many nonspecific medical conditions that fall under the ASIA spectrum (i.e. chronic fatigue, myalgias, and cognitive impairments) are frequently disabling and negatively impact individuals’ private and professional activities. The inclusion of this category of adverse manifestations under ASIA is of special importance because in the past they were frequently ignored or disregarded as irrelevant and non-vaccine-related by physicians and patients but also by scientists involved in the design of vaccine trials. Finally the delineation of ASIA further emphasizes the fact that the use of Al adjuvant-containing placebos in vaccine clinical trials can no longer be justified.
Conclusions

Scientific literature and clinical experience show that metals play a key role in the development of autoimmune diseases. Whether metals induce autoimmunity or whether they aggravate existing disease, through removal of sensitizing metals upon identification of metal triggers has improved patient health. Larger randomized studies in susceptible individuals, selected on the basis of genotypic or phenotypic biomarkers, should be pursued in the future, as suggested by Weiss and Liff (1983). Studies of phenotypic markers may be suitable for the elucidation of casual pathways and identification of specific risk factors. The limited power of epidemiological studies to detect minor susceptible populations, such as those susceptible to mercury, has been discussed by Wallach et. al (2003). The benefits of this approach for patients can be monitored not only by the decree in antibodies titers (Sterzl et al., 1999), but also by downregulation of metal-specific lymphocyte responses in vitro (Stejskal et al., 1999, 2006, 2013; Yaqob et al., 2006). Finally the identification of sensitized T cells in human blood can be made use of in future studies of vaccine-induced side effects. Elucidation of the possible mechanisms will contribute not only to successful treatment of affected individuals, but also to the development of safer vaccines. The use of human blood lymphocytes and vaccine research has recently been suggested (Brooks et al., 2014).

Conclusions

These are exciting times in which to be doing research, given the rapid pace of development of high-throughput technologies for clinical and basic use. Methodological approaches are maturing toward systems view for identifying and characterizing immune responses by inspecting different -omics layers of information (e.g. proteomics, transcriptomics, metabolomics, genomics). The ultimate goal for the application of these new technologies would be to identify biomarker signatures, which would show how innate and adaptive responses are to be integrated into a unified network.

The immune response network theory, in its simplest form, is based on the premise “the response to a vaccine is the cumulative result of interactions driven by a host of genes and their interactions, and is theoretically predictable” (Poland et al., 2013). Scientists are nurturing this definition by recognizing and including the impact of epigenetic, metagenomics, and other factors that might influence or play a role in defining the onset of vaccine response (Poland et al., 2013). The main obstacles impairing our ability to predict a response and to develop effective vaccines or treatments are increased genetic variability in the human population and the con-
stant evolution of pathogens. These two effects produce a wide spectrum of possible host-pathogen interactions and compel the use of systemic approach that can disentangle mechanisms and provide a definition of targeted-population and personalized vaccines, hopefully in the near future.

Conclusions

It is currently widely believed that there is no association between silicone, most commonly in the form of silicone breast implants, and specific autoimmune diseases. However, silicone-induced inflammatory fibroproliferative response, namely capsular formation around silicone breast implants, is an irrefutable, well-documented occurrence, and the presence of anti silicon antibodies and non defined silicone-associated autoimmune phenomena seems plausible.

It has been suggested that many studies conducted on the connection between silicone and autoimmunity had several important limitations (Levy et al., 2009):

- Most studies were based on medical records and self-reported data, rather than clinical exams.
- Many studies focused on classically defined autoimmune diseases and did not study other diseases, atypical types of autoimmune diseases, or nondefined immune phenomena.
- Most study samples were too small to meaningfully detect increases in the rare disease they were studying.
- Connective tissue and autoimmune diseases and phenomena may take years to develop and be diagnosed. Most studies had a follow-up period that was too short to allow for the development of immune phenomena or autoimmune diseases. Studies that include women who underwent breast augmentation just a few months or years prior to enrollment cannot determine whether breast implants increase the long-term risk for such diseases.
- Many studies did not specify whether participants had had their implants removed prior to or during the study. This affects the exposure time to silicone, with women who had their implants removed having a shorter exposure than those who kept them.

Future studies that generate long-term data on a wider scale end-points that include specific autoimmune diseases and nondefined autoimmune phenomena should help clarify the presumed association between silicone and autoimmunity.
Conclusions

In conclusion, the clinical experimental and genetic studies allude to the immunogenic role of silicone in susceptible people. This means that silicone is safe and well tolerated in the general population, but may trigger ASIA in patients with a genetically susceptible background.

Autoantibodies Induced by Vaccine

Conclusions

Studies that have investigated autoantibody production following various vaccinations show that induction of various antibodies is possible, but so far none has been able to prove that the induced antibodies have any clinical consequence. In contrast, several case reports and case series report patients developing autoantibodies and autoimmune adverse events following various vaccinations, emphasizing that clinical consequences could develop in isolated cases and should not be overlooked. Putting all the published evidence together, it seems prudent to conclude that there are certain individuals, most likely with a genetic predisposition, who could develop autoimmune adverse events or diseases following the vaccination under certain unfavorable circumstances, including infection, trauma, physical stress, and any other event that might disturb the complex immune system balance.

We must bear in mind that autoimmunity, including production of autoantibodies following infections, vaccinations, and other environmental triggers, is a feature of a healthy immune system and that, fortunately, the immune system has developed safety mechanisms to prevent the development of an overt autoimmune disease in the majority of cases. The long-term clinical consequences of autoantibodies induced by vaccinations are not
ease in the majority of cases. The long-term clinical consequences of autoantibodies induced by vaccinations are not yet known. Due to several environmental factors will influence over the immune system, it seems at present almost impossible to define the importance of vaccine-induced autoantibodies several years after vaccination.

The ASIA Syndrome Registry

Ignasi Rodriguez-Pinto
Department of Autoimmune Disease
Hospital Clinic de Barcelona
Barcelona, Spain

Yehuda Shoenfeld
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel Hashomer, Israel
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Conclusions

A new registry has been created in order to increase our knowledge of a recent proposed syndrome: the ASIA syndrome. This registry will be a scientific tool through which to cluster information on patient seen by many physicians, which until now has not been grouped in a distinct entity. It will enable us to define the disease criteria and discover any association of clinical manifestations, laboratory features and pathology findings.

Vaccination in Autoimmune Diseases

Carla Gonclaves
Division of Rheumatology
Children’s Institute, Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

Schahin Saad
Division of Rheumatology
Children’s Institute, Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

Clovus A. Silva
Pediatric Rheumatology Unit
Children’s Institute, Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

Eloisa Bonfa
Division of Rheumatology
Children’s Institute, Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

Introduction

Patients with autoimmune rheumatic disease (ARDs) are at increased risk of infection attributed to the underlying disease immunosuppression and treatment immunomodulatory effect (Wolfe et al., 1994; Doran et al., 2002; Bosch et al. 2006; Falagas et al., 2007). Vaccination is an attractive method by which to prevent such infections, including influenza, invasive pneumococcal diseases, herpes zoster, and human papillomavirus (HPV) (van Assen et al., 2011a). However efficacy in patients with ARD may be reduced, and there is a potential risk of flares following vaccination. In addition, adjuvanted vaccines have been reported to trigger autoantibodies and autoimmune/inflammatory syndrome induced by adjuvants (ASIA) (Shoenfeld and Agmon-Levin, 2011). This Chapter will update our knowledge of the efficacy and safety of vaccination in patients with ARD and provide vaccine recommendations for such patients (Table 11.1).
**PART 2  Studies of Autoimmune Conditions Induced by Vaccination**

**CHAPTER 12**

**Vaccination in Patients with Autoimmune Inflammatory Rheumatic Diseases**

**Abdulla Watad**  
Zabludowicz Center for Autoimmune Diseases and  
Department of Internal Medicine B  
Sheba Medical Center  
Tel Aviv, Israel

**Alessandra Soriano**  
Zabludowicz Center for Autoimmune Diseases  
Sheba Medical Center  
Tel Aviv, Israel

**Yehuda Shoenfeld**  
Zabludowicz Center for Autoimmune Diseases  
Sheba Medical Center  
Tel Hashomer, Israel  
Sackler Faculty of Medicine  
Tel Aviv University  
Tel Aviv, Israel

**Introduction**

Vaccines represent the most effective way of preventing morbidity and mortality associated with infections, in healthy as immunocompromised subjects. Patients with autoimmune inflammatory rheumatic diseases (AIRDs) are at increased risk of contracting infections, especially in the course of immunosuppressive treatment. Thus, in the last few decades, several studies have summarized the risk of infection in AIRD and the related benefits of immunization.

On the other hand, several observations underline that the real efficacy of vaccines in subjects with AIRD may be reduced. Moreover, vaccine safety, which is a pivotal issue, may also be reduced, because of the risk of AIRD flare following vaccinations.

In this chapter, we reviewed the main evidence for the risk of infections in patients affected by AIRD, the safety and efficacy of the vaccines in this category of patients, and the current recommendations about who should be vaccinated.

**PART 2  Studies of Autoimmune Conditions Induced by Vaccination**

**CHAPTER 13**

**Measles, Mumps, and Rubella Vaccine: A Triad to Autoimmunity**

**Carlo Perricone**  
Rheumatology, Allergology, and Clinical Immunology  
Department of Internal medicine  
University of Rome Tor Vergata  
Rome, Italy

**Guido Valesini**  
Rheumatology, Department of Internal and Specialized Medicine  
Sapienza University of Rome  
Rome, Italy

**Yehuda Shoenfeld**  
Zabludowicz Center for Autoimmune Diseases  
Sheba Medical Center  
Tel Hashomer, Israel  
Sackler Faculty of Medicine  
Tel Aviv University  
Tel Aviv, Israel
**Conclusions**

It is clear that, excluding exceptional reports (two cases each) of anterior uveitis, retinopathy, vasculitis, and myositis, most adverse events following MMR vaccination involve the nervous system, joints, and blood-related disorders (i.e. ITP) (Table 13.1). It is noteworthy that such kinds of disease reflect the spectrum of autoimmune manifestations that may occur following MMR virus infections (Agmon-Levin et al., 2009b). There are a number of plausible mechanisms that might account for vaccine-induced auto immunity, including the fact that the MMR vaccines are composed of infectious antigens, immune adjuvants, and preservatives, and other ingredients that may trigger the development or exacerbation of our immune phenomena (Colafrancesco et al., 2013). Vaccines are an essential part of preventative modern medicine, but the potential for them to trigger the ASIA syndrome in susceptible individuals should not be ignored. Further efforts should also be made to better investigate the long-term safety of routinely used vaccines (Shoenfeld and Agmon-Levin, 2011; Perricone et al. 2013).

**Yellow Fever Vaccine and Autoimmunity**

**CHAPTER 14**

Roger A. Levy  
Faculty of Medical Sciences  
Rio De Janeiro State University  
Rio de Janeiro, Brazil

Rodrigo Poubel V. Rezende  
Faculty of Medical Sciences  
Rio de Janeiro State University  
Rio de Janeiro, Brazil  
Brazilian Society of Rheumatology  
Rio de Janeiro, Brazil

**Conclusions**

Large-scale YF immunization has been very effective, due to its excellent immunogenicity and safety profile. Every nonvaccinated person living in or traveling to an endemic YF area should be offered the vaccine. Vaccination risk assessment should weigh the odds of acquiring YF (e.g. location, season, duration of exposure, occupational and recreational activities, and local rate of virus transmission) against the odds of experiencing an SAE following YF vaccination. One rational approach would be to measure the serum levels of specific neutralizing IgG antibodies when the lag time of the primary YF vaccination has exceeded 10 years and then revaccinate those who did not sustain protective values. However, this does not seem mandatory, as studies have demonstrated that the majority of YF vaccinated people exhibit immunological response for decades.
**Antiphospholipid Syndrome and Vaccines**

**CHAPTER 15**

**Miri Blank**  
Zabludowicz Center for Autoimmune Diseases  
Sheba Medical Center  
Tel Hashomer, Israel

**Paola Cruz-Tapias**  
Doctoral Program in Biomedical Sciences  
Del Rosario University  
Bogota, Columbia

**Conclusions**

All of the evidence points to the association between diverse vaccines and APS. Molecular mimicry has been proposed as one of the mechanisms by which experimental APS can occur in association with pathogens. Sequence similarities between foreign proteins (i.e., TTd) and self-proteins are sufficient to trigger a loss of immune tolerance, either by molecular mimicry or by bystander-effect mechanisms, resulting in the formation of pathogenic autoantibodies related to APS.

**Hepatitis B Vaccination and Autoimmunity**

**CHAPTER 16**

**Daniel S. Smyk**  
Institute of Liver Studies  
King’s College London School of Medicine  
King’s College Hospital  
London, UK

**Dimitros P. Bogdanos**  
Institute of Liver Studies  
King’s College London School of Medicine  
King’s College Hospital  
London, UK  
Department of Medicine  
School of Health Sciences  
University of Thessaly

**Yehuda Shoenfeld**  
Zabludowicz Center for Autoimmune Diseases  
Sheba Medical Center  
Tel Hashomer, Israel  
Sackler Faculty of Medicine  
Tel Aviv University  
Tel Aviv, Israel

**Lazaros I. Sakkas**  
Department of Medicine  
School of Health Sciences  
University of Thessaly  
Larissa, Greece

**Conclusions**

Although rare, autoimmune conditions related to HBV vaccine do appear to occur in some predisposed individuals. Data regarding HBV vaccine and most autoimmune conditions are scarce, which does not allow definitive conclusions to be drawn. However, several conditions do we have a large number of case reports, in addition to larger studies. Links appear to be strongest in regards to MS and myelitis, vasculitis, chronic arthritis, SLE, and thrombocytopenia/pancytopenia. However, it must be noted that even these incidents are exceedingly rare, and vaccination is still recommended, especially in at-risk individuals. Development of vaccines lacking autoimmunity-prone adjuvants (Saade et al., 2013) (such as aluminum) could further minimize the risk for development of HBV vaccine-induced autoimmune phenomena.
Conclusions

Vaccines are given to healthy people for the prevention of diseases they may never encounter in their lifetimes, and, as such, they need to be held to the highest safety standards possible. The human clinical trial data for the two HPV vaccines currently on the market to reveal a troubling safety profile that requires an accurate reevaluation of the risks and benefits. The HPV vaccines do not replace currently available methods for screening or treating cervical cancer, and their effectiveness in preventing any cancer death will not be seen for several decades. Given that the death rate from cervical cancer in 9 to 20-year-old girls is zero, the short-term risks from the vaccine to otherwise healthy individuals seem to significantly outweigh the as yet unproven long-term benefits (Gerdhaus and Razum, 2010; Tomljenovic and Shaw; 2012b; Tomljenovic et al., 2013). Recommendations for the continued use of HPV vaccine should be urgently and accurately reassessed and new guidelines should be requested on the use of appropriate placebos in vaccine safety trials.
Conclusions

1. Influenza infection can be mild or severe and can even cause death, especially in vulnerable population groups. The complications observed in patients with influenza are caused not only by the severity of the infection, but also by the development of opportunistic infections, as well as by the inadequate and untimely immune response especially in AIRD.
2. The best preventative measure that we currently have is a vaccine. In order to avoid complications or onset of ASIA, the use of nonadjuvanted vaccine is recommended.
3. The medical committee should be alert and report any side effects, including the onset or activation of AIRDs associated with or related to the influenza vaccine.
4. Even though the autoimmune diseases ASIA have been described in patients with influenza A (H1N1) vaccine, the benefits of immunization still outweigh the risks.

Conclusions

We can conclude that meningococcal vaccines do not cause autoimmune diseases this but may unmask autoimmune phenomena in rare individuals, who probably carry an unknown genetic predisposition. According to the CDC, persons at increased risk for meningococcal disease, for whom immunizations is therefore recommended (Cohn 2013), are:

- College freshmen living in dormitories.
- Microbiologists routinely exposed to N. meningitides.
- Populations in which an outbreak of meningococcal disease occurs.
- Military recruits.
- Persons with increased susceptibility (those with anatomical or functional asplenia or terminal complement deficiency).
- Travelers to region where meningitides is hyperendemic (e.g. sub-Saharan Africa and Saudi Arabia) or epidemic.
- People with a history of GBS who are not in a high-risk group for invasive meningococcal disease should not receive MCV4, although, in 2010 the ACIP removed precautionary language from its recommendations, since recent studies had not shown an increased risk of GBS in individuals receiving Menactra (CDC, 2011).
Results

We have not found any epidemiological study investigating specifically autoimmune adverse events post-pneumococcal vaccination. However, during a period of 33 years (1980-2013), only 14 case reports addressed the plausibility of the appearance of rheumatic disorders following immunization with a pneumococcal vaccine (table 20.1). Among these, six reports described reactivation of an autoimmune disorder following immunization with pneumococcal vaccine. Three subjects had some kind of autoimmune reaction after previous vaccination. The mean age of the patients was 50 (the youngest was 17 years old, the oldest was 87), and nine subjects (64.3%) were men. The autoimmune disorders reported in the 14 cases can be divided into dermatological, neurological, and hematological phenomena. Intriguingly, almost all the reported cases are related to the nonadjuvanted 23-valent vaccine, which has been on the market for the last 3 decades.

In addition, several studies of larger cohorts have been performed in order to define the safety of pneumococcal vaccine among patients with autoimmune diseases (Klippel et al., 1979; Battafarano et al., 1998; Elkayam et al., 2002, 2007; Tarjan et al., 2002; Pisoni et al., 2003; Heijstek et al., 2011; Shunsule et al., 2013). These studies followed a total of 313 adults with SLE and 98 with RA. The results showed pneumococcal immunization was safe, with a smaller profile of adverse reactions than the one observed among healthy subjects. Moreover, the EULAR recommendation about vaccine in pediatric populations concluded that pneumococcal vaccines were safe for children with autoimmune disorders (Heijstek et al., 2011).
Introduction

The Bacillus Calmette-Guerin (BCG) is a live, attenuated vaccine from Mycobacterium bovis obtained by Albert Calmette and Camille Guerin through 230 in vitro passages between 1908 and 1921, when it was first used in Paris. Since then, BCG has been distributed all over the world as a preventive tool against tuberculosis (TB), although its use has changed over time as different epidemiological conditions have arisen, and despite debate about its preventive effect reaching only 51% risk reduction. Indeed, the BCG vaccination shows a positive protection on extrapulmonary TB and mortality in children but has a variable and only partial prevention against pulmonary disease in adults (Colditz et al., 1994; Trunz et al., 2006). Alongside this current main use, other nonspecific immunological effects of BCG have become evident over the years, leading to its application in the clinical management of several diseases (Table 21.1). Since 1976, intravesical instillation of BCG has presented the chief immunotherapy against bladder cancer (Morales et al., 1976), and at present it is an integral and approved part of the management of non-muscle invasive bladder cancer. Other neoplasms, such as colorectal cancer, lung cancer, and melanoma, have been the targets of BCG immunotherapy, especially in the past. Because of their immunologic background, a variety of diseases (asthma, type 1 diabetes, multiple sclerosis (MS), leprosy) have been evaluated for treatment with BCG (Ritz et al., 2013).
Introduction

Immunization of healthy individuals is the most effective way of protecting the public from infections and epidemics and has proven to decrease morbidity and mortality worldwide. Although licensed vaccinations have been proven to be widely safe and effective, there are cases in which they may be associated with adverse effects. Autoimmune manifestations following immunization, though considered a rare side effect, have been documented in otherwise healthy individuals, as have flares in individuals with known autoimmune diseases. Reduced antibody response to vaccinations has also been documented in individuals with autoimmune conditions, and while it has been suggested by some that the underlying disease is the cause of this phenomenon, others have argued that it may result from the concurrent use of medications that affect the immune response in these individuals (Chatham et al., 2012). These autoimmune side effects maybe associated with humoral response to self-antigens, due to molecular mimicry, epitope spread, bystander activation, or polyclonal triggering, and suggest a strong link between infectious agents and autoimmunity whose pathogenesis is characterized by a complex interaction between genetic and immune defects, and environmental and hormonal factors (Colafrancesco et al., 2013). Recently, adjuvants found in various vaccinations have also been suggested to be inducers of immune-mediated condition, aluminum and silicone being the most common (Blank et al., 2012; Colafrancesco et al., 2013). It is important to state that vaccination has been proven to reduce the burden of infectious disease in patients with autoimmune diseases, and, although live-attenuated vaccines are not recommended for profoundly immune-suppressed patients, other vaccines have adequate safety and efficacy profiles in most studies published to date. Moreover, the immune response to live vaccines is variable in these patients but generally adequate, despite concomitant use of immunosuppressive and biological agents. It is thus important to detect individuals who may be at risk of developing adverse effects and to weigh the benefits against the risks, especially in individuals prone to autoimmune conditions. Physicians should be alerted to this potential association, which may have a long latency period and unique presentations, and should be encouraged to report and analyze such cases.

Conclusions

Because the incidence of post-vaccination vasculitides remains very low, vaccinations should not be limited for this reason. However, caution may be required when its used in children with immunologically mediated diseases such as HSP, as well as in adults with a known history of autoimmune disease, for whom a careful risk-benefit assessment is required. Some authors suggest that children with a history of vaccine-induced vasculitides...
should not be revaccinated, but there are no clear guidelines for what is the most appropriate management. It has been suggested that flu vaccines must be contraindicated in subjects with a history of rheumatoid purpura, with previous history of vasculitis after full vaccination, or with active autoimmune rheumatic disease. Further investigations are needed to clarify biological plausibility of post-vaccination phenomena. Thus, surveillance systems and registries can be important tools for retrospective as well as prospective evaluations of cases, and also for establishing research studies aimed at elucidating genetic susceptibility factors.

Nevertheless, in clinical practice, when the suspicion of vasculitis onset is raised, a meticulous history-taking with special emphasis on vaccine history is imperative, so that an appropriate diagnosis can be established early and management can be initiated. Moreover, follow-up is mandatory to verify whether a different prognosis is associated with these diseases. The lack of evidence for other causes of the symptoms and the coincidence regarding the vaccination in most of the cases analyze here strongly supports a casual relationship between the vaccination and the vasculitis onset, especially where a plausible temporal association exists. For this reason, the modal peak in time of the onset has to be carefully examined, in order to detect cases with peak onset within a few days of vaccination (which are more consistent with hypersensitivity reactions) or within weeks or months (which are more consistent with delayed immune reactivity).

**Conclusions**

“Conclusion unavailable.”
Conclusions

Since the birth of medicine, physicians have been classifying patients by covering under the same umbrella those sharing similar clinical features. The term “undifferentiated” has been used to include all those conditions in which a well-defined diagnosis could not be reached. However, in recent years, signs have demonstrated that, in order to create effective treatments, the underlying etiopathogenic mechanism is more important than the clinical picture. This is especially true in the field of immunity. Indeed, when dealing with cancer, the aim of therapy is to destroy the specific demented cell. When dealing with infections diseases, physicians pay less care if the patient has fever or splenomegaly, as the objective is to kill the pathogenic microorganism. However, in the field of autoimmunity, the causes of each disease are multiple, encompassing the “mosaic of autoimmunity.” Most of the pathogenic mechanisms and etiological grounds are unclear, undefined, or at least hard to find.

The discovery (or, rather, the depiction) of ASIA has for the first time changed this view toward the gathering of patients who share a related picture but, more relevantly, are linked by the same pathogenic mechanism: the adjuvant. ASIA and UCTD share a common fate: both are “undifferentiated,” meaning that there is no specific clinical feature characterizing each entity, and both can shift toward a definite autoimmune disease. Indeed, the overlap between the two conditions is evident, as shown in table 25.4. Physicians should not perhaps be dwelling too much on classifying patients, but instead should aim at discovering the mechanisms underlying the pathogenesis of autoimmune disease, as elucidating these mechanisms will be the key to finding effective preventative therapeutic strategies.
Conclusions

Although AA is not life-threatening disease, patients may experience devastating effects on the quality of life and self-esteem. A possible association between vaccination and AA has been suggested by a few case reports concerning different vaccines; the largest case series reports such a link with HBV vaccine (Wise et al., 1997). Further research on the various environmental and genetic factors which may lead to the development of AA and, especially, on the link between AA and permutation is warranted.

Introduction

Over the last century, billions of humans have been vaccinated, and marked regression or eradication of several severe infectious diseases has been observed. Today, the potential applications of vaccines extend far beyond prevention of infectious diseases, and vaccination is considered to be the most promising weapon against a variety of different conditions. In general, vaccine safety has been regarded as excellent at the level of the population (Moxon and Sigriest, 2011), but adverse effects have also been reported (Agmon-Levin et al., 2009). Given the considerable worldwide development of vaccination, safety signals in the field require the attention of the medical and scientific community, even of their intensity seems a priori to be low.

Concerns linked to the rise of aluminum adjuvants (known as alum) have emerged following the recognition of
their role at the origin of the so-called macrophagic myofasciitis (MMF) in 20001 (Gherardi et al., 1998, 2001). MMF reveals a fundamental misconception of their adjuvant effect and points out their unexpectedly long biopersistent (Gherardi et al., 2001). Recent demonstrations of their apparent capacity to migrate in lymphoid organs and to progressively accumulate in the brain (Khan et al., 2013) suggest that alum adjuvant safety should be assessed in the long term, that administration of escalation does of this compound to the population should be avoided, and that individual susceptibility factors to the development of alum adjuvant intolerance should be investigated.

Aluminum Particle Biopersistence, Systemic Transport, and Long-term Safety; Macrophagic Myofasciitis and Beyond

Carlo Perricone
Rheumatology, Department of Internal and Specialized Medicine
Sapienza University of Rome
Rome, Italy

Maurizio Rinaldi
Rheumatology, Allergology, and Clinical Immunology
Department of Internal Medicine
University of Rome Tor Vergata
Rome, Italy

Robert Perricone
Rheumatology, Allergology, and Clinical Immunology
Department of Internal Medicine
University of Rome Tor Vergata
Rome, Italy

Yehuda Shoenfeld
Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center
Tel Hashomer, Israel
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Conclusions

Vaccinations have proved to be great advantage to the general population in preventing the spread of infectious diseases. Vaccine safety has improved improved in recent years, and the incidence of vaccine-induced autoimmunity is rare, but they are not yet free of risk. It is becoming apparent that is not only the active components that could drive autoantibody production, but also the excipients, such as adjuvant (pristine, aluminum, squalene), or even the residual traces of yeast from the manufacturing process (Rinaldi et al., 2013). The course of ITP can be very serious, even leading to fatal intracranial hemorrhages, although usually the platelet count improves spontaneously or normalizes after therapy. Unfortunately, in some patients, especially in adulthood and adolescent, ITP can be chronic disease that must be continually monitored and treated.

Infections are much more likely to trigger ITP than are preventative vaccines. However, it should be borne in mind that preventative vaccines are usually administered to otherwise healthy subjects who are not yet fighting the infectious disease for which they are considered at risk. Thus, we must be careful not to cause harm to healthy individuals. Furthermore, it is critical to recognize that the induction of autoantibodies by any infectious or a vaccine-component trigger, and therefore the onset of autoimmune disease (including ITP) can occur in a period of days or years. While the short latency of post-streptococcal-induced rheumatic fever is a few weeks (Arbuckle et al., 2003). The temporal relation between vaccinations on immunity depends on the particular vaccine used and its associated phenomena. Finally, following from the displaced efficacy of eradication therapy in H. pylori associated ITP, therapy should always be consistent with the principle of removing the pathogenic
Conclusions

The results of many studies do not support an association between vaccination and T1D in either young adults or children. However, available data are incomplete and difficult to interpret, partly because several factors are thought to be involved in the development of T1D. Well-designed and long-term studies into the use of vaccines and an incidence of childhood diabetes are ongoing.
Conclusions

All the evidence mentioned in this chapter suggests an important role for an immune-mediated process induced environmental factors, especially the ASO3-adjuvanted Pandemrix vaccine, in the development of narcolepsy in genetically susceptible populations. However, the precise mechanism by which the ASO3-adjuvanted Pandemrix vaccine or the H1N1 infections itself might induce the onset of the disease is still not clear. There has been much speculation regarding this issue. Singh et al., (2013) have proposed a model, which explains how H1N1 infection or vaccine can induce the loss of orexin neurons, via an interaction between infections and genetic factors (Figure 30.2). Different mechanisms may be involved in this process, including bystander activation of autoreactive B and T cells in response to the vaccine’s adjuvants. Moreover, the HLA association may suggest that antigen presentation of cross-reactive peptides can lead to the activation of the immune response against the orexin neurons. Another explanation is molecular mimicry between orexin neuron molecules and the vaccine, the H1N1 virus, or other infectious agents (e.g. Streptococcus sp.) found to be associated with the development of the disease (Kornum et al., 2011; Singh et al., 2013; Mahlios et al., 2013). Regarding the role of the vaccine, two interesting options have been proposed. First, the AS03 adjuvant may catalyze the molecular mimicry between orexin and neurons and H1N1 molecules, due both to its nature and to its method of immune system activation (Mahlios et al., 2013). Second, the presentation of normal post-vaccinated events, such as fever, may favor the migration of pre-existing auto reactive cells or antibodies through the BBB, leading to loss of orexin neurons (Kornum et al., 2011).

Finally, all the data together support the relationship between the H1N1 vaccine in the development of narcolepsy under certain conditions. Therefore, these observations should raise awareness regarding the risks and benefits of H1N1 vaccination versus non-vaccination (Caplan, 2010). Perhaps in the future the genetic and environmental background of a given individual should be taken into account before making a decision to vaccinate.

Non-nutritional Environmental Factors Associated with Celiac Disease: Infections and Vaccinations

Chapter 31

Aaron Lerner
Pediatric Gastroenterology and Nutrition Unit
Carmel Medical Center
B. Rappaport School of Medicine
Technion- Israel Institute of Technology
Haifa, Israel

Conclusions

CD is an autoimmune disease induced by well-known nutritional environmental factors (nondietary factors are less studied and less well established). Several pathogens are associated with CD, but in none of them have cost-effect associations but been established. Evidence is accumulating for possible role of rotavirus in CD pathogenesis. The rotavirus VP7 shares homology with a celiac peptide and with the autoantigen tTg. Anti-VP7 antibodies are predictive for CDN modulate genes involved in pathophysiology. In view of the role of rotavirus in type 1 diabetes induction, the increased incidence of type 1 diabetes in CD patients, and the relationship between rotavirus, gliadin, and CD, the enigma of the rotavirus vaccine as an inducer of CD is awaiting further exploration. In fact, in a very recent publication, Parez et al. (2014) indicate potential safety concerns around rotavirus vaccination in Europe.
Conclusions

Post-vaccinal PMR remains a very rare entity and further efforts are needed to better identify individuals at risk of developing this particular type of disorder. An accurate clinical history, including vaccine history, is mandatory for all elderly patients fulfilling the diagnostic criteria for PMR, as the rate of many post-vaccine autoimmune and rheumatic disorders - including PMR - may be biased by underreporting. A careful risk-benefit assessment must be performed for patients already diagnosed with PMR who are in clinical remission at the time of clinical evaluation for further immunization.

Undoubtedly, further insight into the pathogenesis of post-vaccination phenomena and the identification of markers of genetic predisposition could be useful in preventing these conditions and in developing personalized and safer vaccines in the future.

Conclusions

ADEM is an acute demyelinating disease of the CNS that usually affects the very young. Although well defined clinically, its pathogenesis remains not fully understood. Its resemblance to other —chronic —demyelinating diseases, and especially MS, raises the possibility of common immunopathogenetic paths. Some might claim that ADEM is to MS what AIDP is to CIDP. In support of this are reports of the “transformation” of ADEM into MS and our increasing knowledge of recurrent or relapsing types of ADEM. Others insist that ADEM is a completely different nosological entity, in terms of pathogenesis, course, and prognosis, and that cases of the “transformation” of ADEM to MS were really just MS from the beginning. There are indeed several clinical and paraclinical parameters that clearly differentiate between the two diseases. ADEM is almost always a post-infectious disease, and molecular mimicry and antibody-mediated autoimmune mechanisms seem to play a crucial role in its pathogenesis. Of special interest is post-vaccination ADEM, which accounts for 5—10% of all ADEM cases. The widespread use of vaccinations in recent years (including new types of influenza vaccines and vaccines against HPV for the prevention of gynecological malignancies) has caused an increase in reported cases of ADEM, often with unique (NMO spectrum-like) manifestations. The central role of adjuvants in post-vaccination ADEM (and related conditions) has lately been highlighted. Treatments with steroids or antibody-targeting modalities usually have a favorable effect, and the prognosis is generally good. However, severe, hyperacute, and even lethal forms of ADEM do exist.
Conclusions
Within the complex etiological scheme evolving for FMS, a variety of environmental exposures have been recognized as or suspected of being potential triggers, presumably capable of instigating central sensitization of the genetically prone individual. Within this context, a variety of vaccinations have been documented as being associated with a range of symptoms at least partially overlapping with FMS, such as widespread musculoskeletal pain and fatigue. GWS poses a unique circumstance in which a multisymptom functional disorder developed among many thousands of healthy young individuals, following exposure to a constellation of environmental and stressful circumstances, including the administration of multiple simultaneous vaccinations within a short period. The current evolution of the ASIA syndrome, as well as intriguing indications regarding a role for previously unrecognized CNS inflammation (e.g. microglia activation) in the pathogenesis of central sensitization and chronic pain, indicates that we may currently be standing on the brink of a new era of understanding of the enigma of chronic pain.

Conclusions
The possible association between vaccines and bullous diseases such as BP and PV is still a matter of debate and is supported only by case reports. Importantly, this plausible association has been related to different vaccines most notably anti-influenza vaccine, dTP, polio, and hepatitis. Further research including long-term follow-up studies, on the various environmental factors that may lead to the development of autoimmune bullous dermatoses and especially in the association between immunization and the development of these diseases warranted
Infectious, Vaccinations, and Chronic Fatigue Syndrome

**CHAPTER 36**

Hussein Mahagna  
Deparment of Medicine B  
Sheba Medical Center  
Tel Hashomer, Israel

**Conclusions**

Except for several case reports, there are no studies that indicate vaccines might have a deleterious effect in patients with Chronic Fatigue Syndrome (CFS). However, it is possible that various vaccines or exposures to various pathogens might take part in the induction of CFS.

Howard Amital  
Deparment of Medicine B  
Sheba Medical Center  
Tel Hashomer, Israel

**Myositis and Vaccines**

**CHAPTER 37**

Ignasi Rodriguez-Pino  
Department of Autoimmune Disease  
Hospital Clinic de Barcelon  
Barcelona, Spain

**Conclusions**

Several authors (Orbach and Tanay, 2009; Stuebgen, 2014) have reviewed the association between vaccine administration the development of inflammatory myopathy, but there are few well-designed studies that have directly addressed this issue. Studies performed to date lack power in some cases and have been unable to find a conclusive association between vaccination and IIM. it is not possible to exclude a relationship between vaccination IIM, however, and vaccines probably do cause IIM in genetically predisposed individuals.