HHS Public Access

Author manuscript

Expert Rev Vaccines. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Expert Rev Vaccines. 2015 July ; 14(7): 935–947. doi:10.1586/14760584.2015.1038249.

Adversomics: a new paradigm for vaccine safety and design

Jennifer A. Whitaker, MD, MSc[1,3,4], **Inna G. Ovsyannikova, PhD**[1,2,3], and **Gregory A. Poland, MD**[1,2,3,4,*]

[1]Mayo Clinic Vaccine Research Group, Mayo Clinic, Rochester, MN 55905, USA

[2]Program in Translational Immunovirology and Biodefense, Mayo Clinic, Rochester, MN 55905, USA

[3]Mayo Clinic Division of General Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA

[4]Mayo Clinic Division of Infectious Diseases, Mayo Clinic, Rochester, MN 55905, USA

Summary

Despite the enormous population benefits of routine vaccination, vaccine adverse events and reactions, whether real or perceived, have posed one of the greatest barriers to vaccine acceptance —and thus to infectious disease prevention—worldwide. A truly integrated clinical, translational, and basic science approach is required to understand the mechanisms behind vaccine adverse events, predict them, and then apply this knowledge to new vaccine design approaches that decrease, or avoid, these events. The term “adversomics” was first introduced in 2009 and refers to the study of vaccine adverse reactions using immunogenomics and systems biology approaches. In this review, we present the current state of adversomics research, review known associations and mechanisms of vaccine adverse events/reactions, and outline a plan for the further development of this emerging research field.

Keywords

Vaccines; Viral Vaccines; Immunogenetics; Genetic Association Studies; Systems Biology; Individualized Medicine; Vaccination; Genomics; Drug-Related Side Effects and Adverse Reactions; Polymorphism; Single Nucleotide

Vaccine Adverse Events and Reactions

The use of vaccines to prevent communicable diseases is among the greatest public health achievements of the 20th century [1]. However, despite technologic advances in developing newer and more efficacious vaccines, systems-level improvements in national immunization programs, and the expansion of these programs to remote corners of the developing world, scientists and healthcare workers worldwide continue to fight the age-old foe of vaccines,

*Author for correspondence: Tel: +1 507 284 4968, Fax +1 507 266 4716, poland.gregory@mayo.edu.

Financial and competing interests disclosure

This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

namely, fear [2–9]. This fear ranges from logical concern and illogical anxieties regarding known vaccine adverse reactions to panic over unproven and imagined sequelae of vaccination [2,4,10–13]. In one case-control study of parental vaccine refusal in the United States, the most common reason for vaccine refusal was fear that the vaccine itself might cause harm (57%) [12].

Prophylactic vaccines are held to greater safety standards than many other drugs and biologic products, principally because they are given to largely healthy populations with the intent to prevent, rather than treat, disease. Vaccines are designed to stimulate an immune response to an antigen, and, in so doing, they often produce inflammatory effects. Usually, these reactions are mild and manifest as mild local or systemic adverse reactions to a vaccine such as redness, swelling, or fever. Uncommonly, the immune response may result in a more severe or prolonged adverse reaction. Rarely, a life-threatening allergic reaction may occur after vaccination. Specific diagnostic criteria for establishing a case of anaphylaxis after immunization have been established [14]. A vaccine adverse reaction is defined by the U.S. Centers for Disease Control and Prevention (CDC) as “an untoward effect caused by a vaccine that is extraneous to the vaccine’s primary purpose of producing immunity” [15]. Vaccine adverse reactions are often termed vaccine side effects. The term “vaccine adverse event” refers to any untoward medical event that occurs following vaccination [15]. An adverse event may be a true adverse reaction that is caused by the vaccine or an unrelated, coincidental event. Investigation is required to determine if the adverse event is caused by the vaccine. The World Health Organization (WHO) has published a manual for causality assessment of adverse events following immunization (AEFI) [16,17]. It is important to perform a systematic evaluation of all possible causes of an AEFI that includes assessment of the temporal relationship, biological plausibility, consideration of alternative explanations (e.g., pre-existing illness, onset of new illness that is not related to immunization, spontaneous occurrence of an event without known risk factors, onset of a genetically programmed disease, recent exposure to another infectious agent or toxin prior to the event, occurrence of the event in the past independent of immunization, possible medication effects), and prior evidence that the vaccine has been shown to cause the particular event [16]. The WHO causality assessment involves a fourstep process of assessing eligibility of an event as an AEFI that results in classification of the event as “consistent causal association to immunization,” “indeterminate,” “inconsistent causal association to immunization” (coincidental), or “unclassifiable” (Table 1) [16]. The association is “indeterminate” when adequate information on the AEFI is available, but it is not possible to assign it to “consistent causal association” or “inconsistent causal association to immunization.” An event is “unclassifiable” when additional information is required to determine causality [16]. Vaccine-product reactions may be related to the vaccine antigen(s), another vaccine component, and adjuvant (if present), or a combination of the vaccine antigen(s) and adjuvant. The frequency of vaccine adverse reactions vary by vaccine type and characteristics of the patient population examined. Vaccines may unmask susceptibility toward a vaccine adverse event in certain populations (e.g., fever after vaccination may result in febrile seizures in children with a predisposition for seizure disorders). Vaccine immunogenicity is influenced by multiple individual patient factors (e.g., age, sex, comorbidities, genetics) and vaccine factors (e.g., antigen dose, vaccine delivery

mechanism, vaccine schedule, and vaccine adjuvant). These factors may also influence inflammatory responses, which may in turn lead to vaccine adverse effects. WHO classifies vaccine product-related and vaccine quality defect-related reactions as those "associated with route or site of administration," "immune-mediated," and "reactions as a consequence of replication of a vaccine associated microbial agent" (Table 1). "Reactions as a consequence of replication of a vaccine associated microbial agent" are more likely to occur in patients who are immunosuppressed. The mechanisms behind these adverse reactions to live vaccines are different than immune-mediated reactions to inactivated vaccines.

Immune-mediated vaccine adverse events that have been found to have a causal association with a vaccine are ideal targets of study for the field of adversomics. Compared to the significant focus on vaccine immunogenicity, less attention has been paid to factors that influence immune-mediated adverse vaccine events and the mechanisms behind these events. Understanding and preventing serious adverse vaccine events is critical to improving public trust in vaccine safety and to developing new safe and effective vaccines. In this regard, much can be gleaned from the fields of personalized medicine and pharmacogenomics to offer a new paradigm for understanding and predicting adverse vaccine events. In turn, these observations may then aid in the design of new vaccines that avoid or decrease the frequency of these vaccine adverse events.

Personalized Medicine, Vaccinomics, and Adversomics

The principles of "personalized medicine" apply equally to "personalized vaccinology"—by which we mean that the choice of the vaccine administered should take into account critical characteristics of the individual. We could administer the right vaccine, at the right dose, for the right patient, at the right time. Not all individuals respond in the same way to vaccines. There is an optimal personalized vaccine approach, consisting of an optimal vaccine formulation, route of administration, adjuvant, dose, and dosing schedule (for vaccines that require multiple doses) for an individual or group of individuals. We have called for the application of "vaccinomics" to help us understand the genetic and non-genetic factors influencing the immune response to a vaccine antigen at the systems level [18–24]. Similarly, we have called for the development of "adversomics"—the application of immunogenomics and systems biology to understand the genetic and non-genetic drivers of vaccine adverse reactions at the molecular level [18,25,26].

The field of pharmacogenomics has demonstrated that exploratory genomics discovery studies can lead to validated biomarkers that can be used to predict risk for adverse drug reactions. One elegant example is the link between the human leukocyte antigen (HLA) HLA*B57:01 and potentially fatal idiosyncratic hypersensitivity to the HIV medication abacavir. Prior to using genetic testing, hypersensitivity reactions occurred in 5–8% of patients within the first six weeks of starting abacavir therapy [27].Shortly after abacavir approval in the United States, an association between abacavir hypersensitivity and HLA-B*57:01 was published, [28,29],replicated, and validated across multiple patient cohorts [30,31]. Further research demonstrated that the precise mechanism by which abacavir . binds non-covalently to the peptide binding groove floor of HLA-B*57:01 and alters the presentation of self-peptides presented to the immune system and activation of CD8+ T-

lymphocytes, which results in the release of inflammatory cytokines that cause the clinical hypersensitivity reaction [32–35]. This specificity explains the 100% negative predictive value of HLA-B*57:01 genetic testing for abacavir hypersensitivity [31], which has resulted in its widespread use and incorporation into U.S. HIV treatment guidelines [36,37]. Other examples of hypersensitivity reactions to particular drugs and specific HLA associations include allopurinol (HLA-B*58:01) and carbamazepine (HLA-B*15:02) [38]. The field of pharmacogenomics is rapidly evolving with further applications of genetic variations beyond idiosyncratic drug reactions to effects on pharmacokinetics, pharmacodynamics, and molecular defects related to the pathogenesis of certain malignancies for which specific targeted treatments have been developed. At this time, no such elegant examples exist for explanations or mechanisms of immunologically medicated vaccine adverse reactions, emphasizing the need for additional research in this field.

Adversomics—Current State of the Field

The field of vaccine adversomics, as we have described it [39], is really an extension of pharmacogenomics. However, when compared to the field of pharmacogenomics (which studies drugs) , the field of vaccine adversomics is in its infancy. At this time, these technologies are not being used clinically. The first step in advancing this science is to use adversomics research techniques to understand the mechanisms behind adverse events that have a causal relationship with immunization. We propose that the same methodologies that have been used to study drugs can and should be applied to the study of vaccines. The precise mechanisms of adverse reactions associated with vaccines are not well understood. Understanding the molecular/genetics/proteomics level (i.e., adversomics) involvement, specifically how genetics (genomics and transcriptomics) impact the development of vaccine adverse reactions, may aid in the design of newer and safer vaccine candidates [25,39]. Table 2 provides a comprehensive review of what has been published in the field of adversomics to date.

Evaluating Causation of Alleged Vaccine Adverse Events—Childhood Immunizations and Seizure Disorders

One important lesson that can be learned from the application of genomics to the study of vaccine adverse events (AEs) is that not all AEs are actually related to the vaccine. A recent study by Verbeek and colleagues demonstrated that, in most cases, genetic or structural defects are the underlying cause of epilepsy onset after routine immunization in children [40]. They examined data for 990 children who experienced seizures following immunization (four doses of DTaP, a dose of MMR and *Haemophilus influenza* type B vaccines) during the first two years of life. Of the 1,022 potential epileptic seizures amongst these 990 children, 68% and 32% occurred after receiving of an inactivated vaccine and live attenuated vaccine, respectively [40]. Following DNA sequencing in 14 (61%) out of 23 children with epilepsy and vaccine-related seizure onset, underlying genetic or structural causes were identified in 15 (65%) of those children. Eleven children had Dravet syndrome associated with the *SCN1A* (sodium channel, voltage-gated, type I, alpha subunit) gene mutation. It was stated that “these underlying causes were not limited to SCN1A–related Dravet syndrome but extended to other genetically determined fever-sensitive epilepsies”

and that “early genetic testing should be considered in all children with vaccination-related onset of epilepsy” [40]. Another study evaluated 14 patients with alleged vaccine-related seizures or seizure disorders in whom the first seizure occurred within 72 hours of vaccination after administration of trivalent diptheria-pertussis-tetanus vaccine or pentavalent diphtheria-pertussis-tetanus-inactivated polio-Haemophilus influenzae type B vaccine. These patients had genetic studies performed that resulted in diagnoses of specific epilepsy syndromes in all 14 cases [41]. These studies provide examples of how genetic testing into the cause of alleged vaccine-related AEs can be important in determining if the adverse event was coincidental or truly related to the vaccine. Such investigations are important for evaluating vaccine safety and also maintaining public trust in vaccine safety.

Adversomics and Smallpox Vaccine

Smallpox remains a bioterrorism concern. Despite smallpox disease eradication in 1980, smallpox vaccination with the vaccinia vaccine is still being administered to some first responders, laboratory researchers, healthcare workers, and military personnel; and AEs from vaccinia virus immunization are still observed. In 2003, the U.S. Department of Health and Human Services employed a smallpox vaccination program that included a comprehensive safety monitoring system among HCWs and first responders. Over 38,000 doses of vaccine were administered and 822 AEs were reported; 100 of these AEs were considered serious [42]. AEs included: myocarditis and/or pericarditis in 21 cases, unexpected ischemic cardiac events in 10 cases, generalized vaccinia in two cases, and one case of postvaccinial encephalitis [42,43]. The smallpox vaccine is contraindicated in persons with eczema and exfoliative skin conditions due to the risk of developing vaccinia eczema vaccinatum, in which case the virus disseminates to cause an extensive vesiculopustular rash with systemic illness. The Centers for Disease Control and Prevention (CDC) recommended that those with underlying heart disease and three or more cardiac risk factors should not be vaccinated. It is important to comprehend the underlying mechanisms of these vaccine AEs so they could be better understood and perhaps predicted, and so large populations would not need to be excluded from vaccination should an event occur that would necessitate mass-vaccination. Furthermore, if these mechanisms were elucidated, this knowledge may enable the development and use of new vaccines—an advancement that may result in avoiding these events altogether.

Several recent studies, as reviewed below, have addressed the association between gene polymorphisms and predisposition for AEs after smallpox vaccination. The first example is a study of local and systemic AEs (i.e., fever, generalized skin eruptions, and lymphadenopathy) following smallpox vaccine [44]. Reif *et al*. conducted two studies of healthy vaccinia-naïve adults (n=85 and n=46 subjects, respectively), who received the Aventis Pasteur smallpox vaccine (APSV) and were evaluated at fixed time points (days 3–5, 6–8, 9–11, 12–15, and 26–30) after vaccine. In the first study of 85 subjects, 16 had systemic AEs; in the second study of 46 subjects, 24 subjects had systemic AEs. All subjects were genotyped for 1,442 SNPs that originated from 386 candidate genes. The investigators found specific SNPs/haplotypes in the *MTHFR* (enzyme 5,10-methylenetetrahydrofolate reductase, non-synonymous rs1801133, $p<0.01$) and *IRF1* (interferon regulatory factor-1, rs9282763 and synonymous rs839, $p=0.03$) genes that were significantly associated with

AEs in both studies [44]. Genetic variants in the *MTHFR* gene have been previously associated with adverse reactions to other pharmacologic biologics [45,46]. As the authors wrote, protein products of the *MTHFR* and *IRF1* genes may play an important role in homocysteine metabolism, as well as roles in regulating endothelial function and activating transcription of the Type I (α and β) and Type II (γ) interferons, respectively.

Cases of myocarditis and myopericarditis after smallpox vaccination have been reported. Smallpox vaccine studies, including studies examining genetic predisposition for AEs after smallpox vaccine, have been conducted in order to examine the mechanisms behind these vaccine adverse events [47–52]. Variola virus, the causative agent of smallpox, does not directly cause cardiovascular complications, but vaccinia virus vaccine (Dryvax, ACAM2000) has been associated with electrocardiogram (ECG) and cardiac enzyme abnormalities and occasionally with signs and symptoms associated with myocarditis and myopericarditis [42,48,49]. It is not understood whether vaccinia-associated myopericarditis is due to direct viral injury, secondary to the immune response, host genetics or a combination of these and other factors in the studied populations. A better understanding of the genetic and immunologic factors related to vaccinia-associated myopericarditis is needed, and such studies are currently being conducted in our laboratory.

The genetic basis for developing fever (defined as a temperature >37.7°C) after smallpox (Dryvax) vaccination has been evaluated [53]. A total of 357 SNPs in 19 immune-related genes were examined for each of the 346 healthy study subjects after vaccination with live vaccinia virus vaccine. This study found that specific haplotypes in the *IL1* and *IL18* genes are associated with the development of fever and differences in humoral immunity after smallpox vaccine. The exact mechanisms are not known, but in a mouse model of coxsackie virus-induced myopericarditis, elevated levels of IL-1 and IL-18 cytokines have been related to myocardial inflammation, and inhibition of IL-1 action (using IL-1 receptor antagonist) improved both inflammation and mortality [53,54]. In addition, this study identified a haplotype in the *IL4* gene that was highly significant for its association with decreased likelihood of fever after vaccine in vaccinia vaccine naïve subjects. This *IL4* haplotype includes the SNP rs2243250 that is associated with augmented secretion of an important Th2 regulatory cytokine, IL-4, known to inhibit IFN-γ production and Th1 response [55,56]. In a study of 580 healthy Caucasian individuals (19–40 years old) after a single dose of Dryvax vaccine, genetic variation in the *IL1R, IL18*, and *IL18R1* genes was linked to vaccinia-specific IL-1β production [57]. We believe that functional studies of genetic variants are needed to gain knowledge into the mechanisms by which these SNPs/haplotypes contribute to smallpox vaccine immunity and vaccine-associated AEs. The potential involvement of *IL1, IL18, IL4* and other genes in AEs associated with the administration of other vaccines (e.g., MMR, MMRV, yellow fever, hepatitis B, influenza, anthrax, etc.) is of great interest and should also be further investigated.

Adversomics and Yellow Fever Vaccine

The live attenuated yellow fever vaccine 17D (YF-17D) is a well-tolerated vaccine with very few known cases of vaccine-associated AEs. However, there is a rare, but serious, risk of severe yellow fever-like disease due to the vaccine strain of the virus. Yellow fever

vaccine 17D–induced viscerotropic disease is a serious vaccine AE characterized by multiple- organ system failure that has a high fatality rate [58,59]. It has been suggested that yellow fever vaccine-associated viscerotropic disease is associated with persistent viremia, robust induction of T and B cell responses, and polymorphisms in the chemokine receptor *CCR5* (delta 32) and its ligand *RANTES* (403G/A) genes [58]. Further, Bae *et al*. noted that serum cytokines and chemokines, such as RANTES, IL-6, IL-8, MIG (monokine induced by IFN-γ), GRO (growth-related oncogene), MCP-1 (monocyte chemotactic protein), TGF-β (transforming growth factor), and TNF-β (tumor necrosis factor) may be considered as surrogate markers for individuals likely to develop severe yellow fever-associated AEs, such as vaccine-associated neurotropic and viscerotropic diseases [60]. It is possible that increased and/or decreased production of these biological markers, due to polymorphisms in these genes, may have impaired the immune response to YF vaccine. On the other hand, Martins *et al*. studied 50 subjects vaccinated with 17DD YF vaccine and reported that an increased frequency of circulating CD4+HLA-DR+ (and CD8+CD69+) cells at day 7 post-vaccination, and CD8+HLA-DR+ lymphocytes at day 30 post-vaccination may be reliable markers for an immune response that is free of AEs after YF vaccination [61]. These studies provide initial insights into yellow fever vaccine AEs; however, we are a long way from understanding the mechanisms behind these AEs or being able to predict them.

Adversomics and Influenza Vaccine

Guillain-Barré Syndrome

Although the risk of Guillain-Barré syndrome (GBS) following influenza vaccination has been shown to be lower than after influenza illness [62], there is still significant public concern regarding vaccination leading to this neurologic condition. Immune response to microbial antigens that are cross-reactive with neural epitopes may trigger an inflammatory disorder – GBS--in which genetic host factors may impact disease susceptibility. In 1976–1977, there was an increased risk of GBS following vaccination with the swine influenza vaccine, with an estimated attributable risk of GBS after vaccine in adults of just under 1 case per 100,000 vaccinations and a relative incidence (RI) of 7.6 (95% CI, 6.7–8.6) [63,64]. The precise reason for this relationship is not known. Recently, the effects of gene polymorphisms on GBS risk have been recognized for several genes: *TNF*-α (tumor necrosis factor-alpha) gene (polymorphisms 308 G/A and 857 C/T), *TLR4* (toll-like receptor 4) gene (Asp299Gly and Thr399Ile), *FcRL3* (Fc receptor like 3) gene (FcRL3-3–169C, FcRL3–6 intron3A, and FcRL3–8 exon15A), and *MMP9* (matrix metalloproteinase 9) gene (C-1562T) [65–68]. However, these studies examined populations with GBS without examining potential inciting causes, such as recent infections or receipt of other vaccines. It is difficult to know if these polymorphisms would predict GBS cases that might result from cross-reactive antigens from different infections or vaccines. These polymorphisms should be explored in relationship to GBS that has occurred after vaccination.

Narcolepsy

After the 2009–10 influenza A H1N1 pandemic and large vaccination campaigns with the AS03-adjuvanted influenza A H1N1 Pandemrix vaccine in Europe, an increase in the incidence of narcolepsy was reported in Sweden and Finland [69–71]. Narcolepsy is

believed to be an autoimmune disease that is caused by the loss of hypothalamic hypocretin-producing neurons [72]. It has been found to have a strong association with the HLA-DQB*06:02 allele in people of all ethnicities. Using strict diagnostic criteria, 98% of patients with narcolepsy and cataplexy are DQB1*06:02 positive [73,74]. It is important to note that in another case-control study of narcolepsy after AS03-adjuvanted influenza A H1N1 vaccination, the HLA-DQB*06:02 allele was found in 100% of narcolepsy cases (47/47), but also in 35% (20/57) of controls [75]. The presence of this allele may be necessary, but not sufficient to result in the vaccine adverse event. The HLA-DQB1*06:02 allele is present in 13–28% of Caucasian populations; however, the risk of narcolepsy in children vaccinated with Pandemrix who carry this allele is only 1 in 1,600 [76]. It has been hypothesized that the AS03-adjuvanted A/H1N1 vaccine resulted in molecular mimicry with a neuronal autoantigen. One study that provided further support for this hypothesis was later retracted due to an inability to replicate the data [77]. Questions remain as to why one AS03 adjuvanted A/H1N1 (Pandemrix) vaccine seems to have led to an increase in narcolepsy cases, while another AS03 adjuvanted A/H1N1 vaccine (Arepanrix), which was prepared by a slightly different inactivation protocol did not [78]. Further work demonstrated that antibody to Pandemrix-derived nucleoprotein (NP) was increased in patients with narcolepsy and the DQB1*06:02 risk allele of narcolepsy appeared to regulate the anti-NP immune response [75]. The authors of this study hypothesized that the differences in the H1N1 antigens of Arepanrix and Pandemrix could explain the differences in vaccine-attributable risk of narcolepsy between these vaccines and call for the screening of NP derived DQB1*06:02 dependent epitopes [75].

Understanding HLA Gene Effects

The field of adversomics would further benefit from an understanding of HLA gene contributions to vaccine-induced immune responses, including AEs. For example, recombinant hepatitis B vaccine-associated major AEs have been hypothesized as being linked to HLA class II DRB1 alleles/haplotypes (*01:01, *03:01, *04:01,*13:01, *15:01) and HLA class I A2 gene interaction [79]. The authors speculate that the presence of the specific HLA allele can result in activation of cytotoxic CD8+ T cells by HLA-A2 presented hepatitis B surface antigens (HBsAg), causing production of high levels of IFN-γ, TNF, and augmentation of vaccine AEs. In fact, several HLA class II DRB1 alleles/haplotypes are linked to hepatitis B vaccine non-response [80,81]. HLA polymorphisms have also been shown to be related to non- and low-response to measles, mumps, rubella, and anthrax vaccines [82–87]. It has been proposed that susceptibility-related HLA class I and class II alleles may drive the development of vaccine AEs after hepatitis B vaccination [79].

The application of genotype-phenotype knowledge will be critical to developing models of genetic predisposition to vaccine adverse effects. Lin et al. have created an Ontology of Genetic Susceptibility Factors (OGSF) which may provide a framework for genetic susceptibility to vaccine-associated AEs [88]. The OGSF uses genetic studies and accounts for diverse types of genetic susceptibility factors, such as HLA alleles, SNPs, genes, and gene haplotypes, and may be useful for identification of true genetic factors/determinants contributing to the susceptibility to vaccine AEs.

Adversomics Research Challenges

There are multiple challenges in adversomics research. First, as depicted in the aforementioned examples, many vaccine AEs are quite rare. This low frequency makes them difficult to identify and to study. Unlike the case of abacavir hypersensitivity, which occurred in 5–8% of persons treated with the medication, many events occur at the level of a few cases per 100,000 population (i.e., GBS), and some occur at even lower frequency (i.e., YF vaccine-associated neurotropic or viscerotropic disease). Second, it is often difficult to prove causality for a vaccine adverse event. Some conditions or symptoms that have been attributed to vaccines are coincidental and not causal. Reported symptoms that are unrelated to the vaccine (such as in the cases of genetically predetermined epilepsy) can cause confounding of analyses. The difficulty in determining causality makes it difficult to identify which outcomes are truly the ones that need to be investigated. Third, in some countries (for example, in the U.S), the system for reporting vaccine AEs is passive. In the U.S., vaccine adverse events are reported to the Vaccine Adverse Event Reporting System (VAERS), which is a CDC- and Food and Drug Administration (FDA)-sponsored post-marketing vaccine adverse events surveillance system. Many vaccine AEs may never be reported, which limits our ability to identify and study these events. Some other countries have active vaccine adverse events surveillance systems. Fourth, there is no efficient system by which we can obtain samples from persons with proven vaccine AEs. Biobanks have been created for multiple disease conditions, but such repositories do not currently exist for vaccine AEs.

Adversomics and Vaccine Design

We recognize the limitations and challenges with adversomics research. At this point in time, the field is in its infancy. It is currently not practical or cost-effective to perform genotyping on a patient and then select a particular vaccine based on these genomic results. Furthermore, in some cases, as in the example of narcolepsy and Pandemrix, the frequency of the allele associated with the vaccine adverse event may be very common in the population, but only a small percentage of persons with this HLA-type may experience the vaccine adverse event. We are not advocating screening populations for particular HLA types and then withholding vaccination in these persons at this time. Vaccination is important for individuals, but it is also important for the “herd.” While we note that personalized medicine may help us understand and predict who is at risk for vaccine adverse events, we suggest using this science to develop vaccines that are safer for the greater population and can be used to design vaccines that will increase “herd immunity.” It would be more efficient and cost-effective to use adversomics research to elucidate the mechanisms underpinning vaccine AEs and use this understanding to design or “reverse-engineer” new vaccines that minimize or avoid these events. Initial observations from the adversomics studies that we have reviewed suggest that persons with particular HLA types may have increased rates of vaccine adverse events. As has been suggested in the case of Pandemrix vaccination and narcolepsy, there may be particular vaccine epitopes that bind particular HLA molecules and trigger a more exuberant inflammatory response, resulting in increased local and systemic adverse reactions, or recognize “self,” resulting in idiosyncratic adverse reactions. Particular vaccine epitopes may skew the immune response in such a manner that is harmful, rather than helpful. As the fields of structural biology and peptide-

based vaccine research advance, we anticipate that not only will promiscuous peptides that induce optimal immunogenicity across HLA types be selected, but also those that do not recognize “self” and result in immunologically mediated vaccine adverse events. In the case of narcolepsy and Pandemrix, if particular vaccine NP derived DQB1*0:02 epitopes are identified and found to be associated with narcolepsy, then, in the future, rational vaccine design could result in vaccines that avoid the presentation of these epitopes altogether.

Adversomics research extends beyond personalized vaccinology or understanding adverse reactions in only some groups of those vaccinated. Consider the example of vaccines for RSV infection. In the 1960s, a candidate formaldehye-inactivated RSV vaccine was found to enhance RSV infection in some children who experienced infection with wild-type RSV after immunization with this candidate RSV vaccine [89]. Subsequent studies in animal models have suggested that the vaccine-enhanced infection may have been associated with the generation of low-avidity antibodies [90] and an imbalanced T_{H2} response [91,92]. The studies of these adverse vaccine outcomes have informed the structure-based design of new RSV vaccine candidates [93,94].

Some of the known vaccine adverse reactions are lacking from Table 2. For example, consider the association between the rotavirus vaccine Rotashield and intussusception. If the mechanism behind this association had been elucidated, or if those who were at risk for developing intussusception might have been predicted, the story of rotavirus vaccines may have been different. Perhaps it could have led to the development of new vaccines that would have avoided this adverse event altogether [95]; however, these mechanisms have not been elucidated. New rotavirus vaccines have been created, and although the frequency of intussusception is lower than with Rotashield, and the benefits of vaccination far outweigh the very low risk of intussusception that may occur after vaccination, concern still remains for intussusception after rotavirus vaccination [96–98].

The Role of Gender in Vaccine Adverse Events

Vaccine adverse reactions have been reported at greater rates among females for influenza [99–101], measles-mumps-rubella (MMR) [102–105], YF[106] and anthrax vaccines [107]. Females have also demonstrated superior vaccine immunogenicity to multiple vaccines [108], including influenza [99–101], measles [109], mumps [84], rubella [110], hepatitis A [111,112], hepatitis B [112,113], and smallpox [114,115]. The mechanisms behind the more vigorous immune responses noted in females merits further exploration [26] and may provide clues to both increased vaccine AEs and increased vaccine immunogenicity in this sex. It has been proposed that sex-based differences among vaccine responses are not solely based on sex hormones, since these differences have been noted throughout all stages of life —prior to, during, and after reproductive capacity [26,108]. The effect of genetic differences between sexes, and the role these differences play in differential immune responses to vaccines, has not been fully elucidated and warrants further investigation. It might also be that females respond more vigorously to certain vaccines and require lower doses than their male counterparts. A pertinent example of an observational clinical study with varying methodologies that provides fodder for further studies is the CDC anthrax vaccine adsorbed (AVA) human clinical trial. [107]. Analysis of data from this trial demonstrated that female

and Caucasian participants had a higher proportion of AVA AEs, as well as higher vaccine immunogenicity (i.e., anti-protective antigen IgG titers) [92].

The Role of Age in Vaccine Adverse Events

Limited data exist on vaccine safety and AEs in aging population, as signs of immunosenescence are observed in this age group [101,116,117]. A review of VAERS data from 2003–2013 did not find any safety concerns for MMR vaccine in adults 19 years old and older [118]. However, in contrast to other vaccines, the YF-17D vaccine may be more frequently associated with viscerotropic AEs in older individuals [58]. The rate of YF vaccine-associated systemic AEs in individuals aged 65 or older was 2.5 times higher than the rate of AEs occurring in younger individuals (25–44 years old) [119]. With regard to influenza vaccine, systemic symptoms among older individuals (≥ 65 years old) were more frequent following vaccination with high-dose (HD) trivalent, inactivated influenza vaccine (180 mcg of HA antigen) compared with a standard dose of 45 mcg [120]. It is possible that adversomic profiles may change with age.

The Rise of Adjuvants

There has been particular concern among some groups regarding adjuvanted vaccines and their potential to cause vaccine adverse reactions. Vaccine adjuvants have been purported to cause or worsen various autoimmune inflammatory conditions. The U.S. has lagged behind many other countries in the approval of various adjuvanted vaccines. As more adjuvanted vaccines enter the markets worldwide, particular attention must be paid to whether they are associated with vaccine adverse events. If vaccine adverse events are noted, then further studies will need to be conducted to determine whether the adverse event is related to the adjuvant, to the antigens in the vaccine, or to an adjuvant-antigen combination.

International Collaboration

International partnerships between clinicians, public health officials, epidemiologists, and clinical, translational, and basic science researchers are needed to advance the field of adversomics. In order to overcome some of the current challenges to the field, we propose the creation of a unifying infrastructure that will monitor vaccine AEs, solicit biospecimens from patients who experience these AEs, and maintain a “biobank” of these specimens for research. There are multiple agencies in the U.S. that are studying and monitoring vaccine AEs and safety, including the CDC, Vaccine Analytic Unit with Department of Defense (DOD), The FDA’s Center for Biologics Evaluation and Research (CBER), the Military Vaccine Agency (MILVAX) within DOD, and individual manufacturers [25]. We propose a broader, coordinated, and more cohesive infrastructure.. The oversight of all of these efforts must be coordinated and infrastructure for such an effort must be built, but we cannot stop here.

As we are reminded daily, particularly with transmission of infections across countries and continents, we live in a global community. In order to determine the rates, associations, causality, and mechanisms behind vaccine AEs, particularly the rare ones, we need an international effort of regulatory, clinical, and scientific teams working together to demystify such events. The Brighton Network [121] and WHO Global Vaccine Safety

Initiative [122] are examples of collaborative international networks focused on vaccine safety research. Such international collaborative networks could be platforms for adversomics research. Through combining the spectrum of clinical, translational, and basic science research across the globe toward the goal of advancing adversomics, new knowledge will be uncovered that may identify individual risk factors, enlarge our understanding of immune mechanisms, and define biomarkers of risk and immunity that can assist in optimizing the development of new vaccines, diagnostic tests, and therapeutics to protect humans from infectious diseases.

Expert Commentary and Five-Year View

Future directions for adversomic research include understanding the role of female biologic sex in vaccine AEs, as females frequently have higher rates of vaccine AEs, evaluation of age and immunosenesce as a risk factor for vaccine AEs, careful attention to the role of adjuvants, and development of international collaborations and biobanks for this research.

Moreover, the promise of adversomics is to understand the mechanisms behind vaccine adverse events in order to improve vaccine safety and to personalize our approach—offering the right vaccine, at the right dose, at the right time, to the right person. Such an approach offers both safety and economic benefits. Such mechanistic information may also inform new vaccine discovery efforts.

Over the next five years, for adversomics research to move from its infancy, researchers from across the translational science spectrum need to partner together; vaccine AEs with causal associations to current licensed vaccines must be identified and thoroughly investigated; international biobanks of samples from those with vaccine-related AEs needs to be created; and immunogenetic and systems biology studies need to be conducted utilizing these samples. OMICS technologies will continue to adapt and advance. Our thinking and research methods will need to do so, as well, if we aspire to rationally design vaccines that will maximize immunogenicity and effectiveness, while minimizing adverse events.

Acknowledgments

The authors were supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health under award numbers U01AI089859, N01AI40065, R37AI048793, and R01AI033144. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. GA Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. GA Poland offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Sanofi Pasteur, Dynavax, Novartis Vaccines and Therapeutics, PAXVAX Inc, Emergent Biosolutions, Adjuvance, and Vaxness. GA Poland and IG Ovsyannikova hold two patents related to vaccinia and measles peptide research. JA Whitaker receives funding for Mayo Clinic research from Pfizer Independent Grants for Learning and Change. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

References

Reference annotations

* Of interest

** Of considerable interest

1. Centers of Disease Control and Prevention. Ten great public health achievements--United States, 1900–1999. MMWR Morb.Mortal.Wkly Rep. 1999; 48(12):241–243. [PubMed: 10220250]
2. Poland GA, Jacobson RM. The age-old struggle against the antivaccinationists. N.Engl.J Med. 2011; 364(2):97–99. [PubMed: 21226573]
3. Tafuri S, Gallone MS, Cappelli MG, Martinelli D, Prato R, Germinario C. Addressing the anti-vaccination movement and the role of HCWs. Vaccine. 2014; 32(38):4860–4865. [PubMed: 24262311]
4. Poland GA, Jacobson RM. The clinician's guide to the anti-vaccinationists' galaxy. Human Immunology. 2012; 73(8):859–866. [PubMed: 22504410]
5. Poland GA, Jacobson RM, Ovsyannikova IG. Trends affecting the future of vaccine development and delivery: The role of demographics, regulatory science, the anti-vaccine and consumer culture and vaccinomics. Vaccine. 2009; 27(25–26 Special Issue SI):3240–3244. [PubMed: 19200833]
6. Larson HJ, Jarrett C, Eckersberger E, Smith DM, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. Vaccine. 2014; 32(19):2150–2159. [PubMed: 24598724]
7. Dube E, Gagnon D, Nickels E, Jeram S, Schuster M. Mapping vaccine hesitancy-Country-specific characteristics of a global phenomenon. Vaccine. 2014; 32(49):6649–6654. [PubMed: 25280436]
8. Larson HJ, Smith DM, Paterson P, et al. Measuring vaccine confidence: analysis of data obtained by a media surveillance system used to analyse public concerns about vaccines. The Lancet. Infect Dis. 2013; 13(7):606–613. [PubMed: 23676442]
9. Ropeik D. How society should respond to the risk of vaccine rejection. Hum Vaccin Immunother. 2013; 9(8):1815–1818. [PubMed: 23807359]
10. Salmon DA, Moulton LH, Omer SB, deHart MP, Stokley S, Halsey NA. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. Arch Pediat Adolesc Med. 2005; 159(5):470–476.
11. Amanna I, Slifka MK. Public fear of vaccination: separating fact from fiction. Viral Immunol. 2005; 18(2):307–315. [PubMed: 16035942]
12. Salmon DA, Sotir MJ, Pan WK, et al. Parental vaccine refusal in Wisconsin: a case-control study. WMJ. 2009; 108(1):17–23. [PubMed: 19326630]
13. Poland GA, Jacobson RM. Understanding those who do not understand: a brief review of the anti-vaccine movement. Vaccine. 2001; 19:2440–2445. [PubMed: 11257375]
14. Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31):5675–5684. [PubMed: 17448577]
15. Atkinson, W.; Wolfe, C.; Hamborsky, J., editors. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Washington, D.C.: Public Health Foundation; 2012.
16. World Health Organization. [Date accessed, February 4, 2015] Causality Assessment of an Adverse Event Following Immunization (AEFI). 2013. http://www.who.int/vaccine_safety/publications/gvs_aefi/en/
17. Tozzi AE, Asturias EJ, Balakrishnan MR, Halsey NA, Law B, Zuber PL. Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use. Vaccine. 2013; 31(44):5041–5046. [PubMed: 24021304]
18. Poland GA, Kennedy RB, McKinney BA, et al. Vaccinomics, adversomics, and the immune response network theory: Individualized vaccinology in the 21st century. Semin Immunol. 2013; 25(2):89–103. [PubMed: 23755893] ** This article provides a review on the applications of vaccinomics and its application to studying vaccine adverse events (adversomics).
19. Haralambieva IH, Poland GA. Vaccinomics, predictive vaccinology and the future of vaccine development. Future Microbiol. 2010; 5:1757–1760. [PubMed: 21155658]
20. Poland GA, Ovsyannikova IG, Kennedy RB, Haralambieva IH, Jacobson RM. Vaccinomics and a new paradigm for the development of preventive vaccines against viral infections. Omics. 2011; 15(9):625–636. [PubMed: 21732819]

21. Poland GA, Oberg AL. Vaccinomics and bioinformatics: accelerants for the next golden age of vaccinology. Vaccine. 2010; 28(20):3509–3510. [PubMed: 20394850]
22. Poland GA, Ovsyannikova IG, Jacobson RM. Application of pharmacogenomics to vaccines. Pharmacogenomics. 2009; 10(5):837–852. [PubMed: 19450131]
23. Poland GA. Pharmacology, vaccinomics, and the second golden age of vaccinology. Clin Pharmacol Ther. 2007; 82(6):623–626. [PubMed: 17998905] ** This paper summarizes the new vaccinomics approach for vaccine development.
24. Poland GA, Ovsyannikova IG, Jacobson RM, Smith DI. Heterogeneity in vaccine immune response: the role of immunogenetics and the emerging field of vaccinomics. Clin Pharmacol Ther. 2007; 82(6):653–664. [PubMed: 17971814]
25. Poland GA. Vaccidents and adversomics. Vaccine. 2010; 28(40):6549–6550. [PubMed: 20831978] ** This article provides a rationale for the development of the adversomics field.
26. Klein SL, Poland GA. Personalized vaccinology: one size and dose might not fit both sexes. Vaccine. 2013; 31(23):2599–2600. [PubMed: 23579257]
27. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther. 2001; 23(10):1603–1614. [PubMed: 11726000]
28. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359(9308):727–732. [PubMed: 11888582]
29. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002; 359:1121–1122. [PubMed: 11943262]
30. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. Clin Infect Dis. 2006; 43(1):99–102. [PubMed: 16758424]
31. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008; 358(6):568–579. [PubMed: 18256392]
32. Ostrov DA, Grant BJ, Pompeu YA, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc Natl Acad Sci USA. 2012; 109(25):9959–9964. [PubMed: 22645359]
33. Illing PT, Vivian JP, Dudek NL, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature. 2012; 486(7404):554–558. [PubMed: 22722860]
34. Martin AM, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. Proc Natl Acad Sci USA. 2004; 101(12): 4180–4185. [PubMed: 15024131]
35. Almeida CA, Martin AM, Nolan D, et al. Cytokine profiling in abacavir hypersensitivity patients. Antivir Ther. 2008; 13(2):281–288. [PubMed: 18505179]
36. Panel on Antiretroviral Guidelines for Adults and Adolescnets. [Date accessed, December 4, 2014] Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf
37. Gunthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA. 2014; 312(4):410–425. [PubMed: 25038359]
38. Chessman D, Kostenko L, Lethborg T, et al. Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of a systemic drug hypersensitivity. Immunity. 2008; 28(6):822–832. [PubMed: 18549801]
39. Poland GA, Ovsyannikova IG, Jacobson RM. Adversomics: the emerging field of vaccine adverse event immunogenetics. Pediatr Infect Dis J. 2009; 28(5):431–432. [PubMed: 19395950] * Important editorial commentary regarding the genetic predisposition for adverse events after vaccination.
40. Verbeek NE, Jansen FE, Vermeer-de Bondt PE, et al. Etiologies for seizures around the time of vaccination. Pediatrics. 2014; 134(4):658–666. [PubMed: 25225143] * This study demonstrates that genetic and structural defects may trigger epileptic seizures after vaccination.

41. Berkovic SF, Harkin L, McMahon JM, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurol. 2006; 5(6):488–492. [PubMed: 16713920]
42. Casey CG, Iskander JK, Roper MH, et al. Adverse events associated with smallpox vaccination in the United States, January-October 2003. JAMA. 2005; 294(21):2734–2743. [PubMed: 16333009]
43. Poland GA, Neff JM. Smallpox vaccine: problems and prospects. Immunol Allergy Clin North Am. 2003; 23(4):731–743. [PubMed: 14753389]
44. Reif DM, McKinney BA, Motsinger AA, et al. Genetic basis for adverse events after smallpox vaccination. J Infect Dis. 2008; 198(1):16–22. [PubMed: 18454680] ** This replication study identifies SNPs in the MTHFR and IRF1 genes that are associated with systemic adverse events after smallpox vaccine.
45. Urano W, Taniguchi A, Yamanaka H, et al. Polymorphisms in the methylenetetrahydrofolate reductase gene were associated with both the efficacy and the toxicity of methotrexate used for the treatment of rheumatoid arthritis, as evidenced by single locus and haplotype analyses. Pharmacogenetics. 2002; 12(3):183–190. [PubMed: 11927833]
46. El-Khodary NM, El-Haggar SM, Eid MA, Ebeid EN. Study of the pharmacokinetic and pharmacogenetic contribution to the toxicity of high-dose methotrexate in children with acute lymphoblastic leukemia. Med Oncol. 2012; 29(3):2053–2062. [PubMed: 21644011]
47. Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. Vaccine. 2005; 23(17–18):2078–2081. [PubMed: 15755574]
48. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. Jama. 2003; 289:3283–3289. [PubMed: 12824210]
49. Wilson CB, Marcuse EK. Vaccine safety--vaccine benefits: science and the public's perception. Nat Rev Immunol. 2001; 1(2):160–165. [PubMed: 11905824]
50. Ovsyannikova IG, Kennedy RB, O'Byrne M, Jacobson RM, Pankratz VS, Poland GA. Genome-wide association study of antibody response to smallpox vaccine. Vaccine. 2012; 30(28):4182–4189. [PubMed: 22542470]
51. Kennedy RB, Ovsyannikova IG, Pankratz VS, et al. Genome-wide genetic associations with IFNgamma response to smallpox vaccine. Hum Gen. 2012; 131(9):1433–1451.
52. Ovsyannikova IG, Pankrantz VS, Salk HM, Kennedy RB, Poland GA. HLA alleles associated with the adaptive immune response to smallpox vaccine: a replication study. Hum Gen. 2014; 133(9): 1083–1092. * This paper demonstrates a basis for the genetic contribution to smallpox vaccine response.
53. Stanley SL Jr, Frey SE, Taillon-Miller P, et al. The immunogenetics of smallpox vaccination. J Infect Dis. 2007; 196(2):212–219. [PubMed: 17570108] * This study demonstrates that fever after smallpox vaccination is associated with IL1, IL4, and IL18 gene polymorphisms.
54. Lim BK, Choe SC, Shin JO, et al. Local expression of interleukin-1 receptor antagonist by plasmid DNA improves mortality and decreases myocardial inflammation in experimental coxsackieviral myocarditis. Circulation. 2002; 105(11):1278–1281. [PubMed: 11901035]
55. Nakashima H, Miyake K, Inoue Y, et al. Association between IL-4 genotype and IL-4 production in the Japanese population. Genes Immun. 2002; 3(2):107–109. [PubMed: 11960309]
56. Nelms K, Keegan AD, Zamorano J, Ryan JJ, Paul WE. The IL-4 receptor: signaling mechanisms and biologic functions. Annu Rev Immunol. 1999; 17:701–738. [PubMed: 10358772]
57. Ovsyannikova IG, Haralambieva IH, Kennedy RB, et al. Impact of cytokine and cytokine receptor gene polymorphisms on cellular immunity after smallpox vaccination. Gene. 2012; 510:59–65. [PubMed: 23009887]
58. Pulendran B, Miller J, Querec TD, et al. Case of yellow fever vaccine--associated viscerotropic disease with prolonged viremia, robust adaptive immune responses, and polymorphisms in CCR5 and RANTES genes. J Infect Dis. 2008; 198(4):500–507. [PubMed: 18598196]
59. Kitchener S. Viscerotropic and neurotropic disease following vaccination with the 17D yellow fever vaccine, ARILVAX. Vaccine. 2004; 22(17–18):2103–2105. [PubMed: 15149765]
60. Bae HG, Domingo C, Tenorio A, et al. Immune response during adverse events after 17D–derived yellow fever vaccination in Europe. J Infect Dis. 2008; 197(11):1577–1584. [PubMed: 18419548]

61. Martins MA, Silva ML, Marciano AP, et al. Activation/modulation of adaptive immunity emerges simultaneously after 17DD yellow fever first-time vaccination: is this the key to prevent severe adverse reactions following immunization? Clin Exper Immunol. 2007; 148(1):90–100. [PubMed: 17309541]
62. Kwong JC, Vasa PP, Campitelli MA, et al. Risk of Guillain-Barre syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study. Lancet Infect Dis. 2013; 13(9):769–776. [PubMed: 23810252]
63. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. Am J Epidemiol. 1979; 110(2):105–123. [PubMed: 463869]
64. Haber P, DeStefano F, Angulo FJ, et al. Guillain-Barre syndrome following influenza vaccination. JAMA. 2004; 292(20):2478–2481. [PubMed: 15562126]
65. Prasad KN, Nyati KK, Verma A, Rizwan A, Paliwal VK. Tumor necrosis factor-alpha polymorphisms and expression in Guillain-Barre syndrome. Hum Immunol. 2010; 71(9):905–910. [PubMed: 20600447]
66. Nyati KK, Prasad KN, Verma A, et al. Association of TLR4 Asp299Gly and Thr399Ile polymorphisms with Guillain-Barre syndrome in Northern Indian population. J Neuroimmunol. 2010; 218(1–2):116–119. [PubMed: 19913922]
67. Sang D, Chen Q, Liu X, et al. Fc receptor like 3 in Chinese patients of Han nationality with Guillain-Barre syndrome. J Neuroimmunol. 2012; 246(1–2):65–68. [PubMed: 22458979]
68. Geleijns K, Emonts M, Laman JD, et al. Genetic polymorphisms of macrophage-mediators in Guillain-Barre syndrome. J Neuroimmunol. 2007; 190(1–2):127–130. [PubMed: 17761309]
69. Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLos ONE. 2012; 7(3):33536.
70. Partinen M, Saarenpaa-Heikkila O, Ilveskoski I, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. PLos ONE. 2012; 7(3):33723.
71. Szakacs A, Darin N, Hallbook T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. Neurology. 2013; 80(14):1315–1321. [PubMed: 23486871]
72. Fontana A, Gast H, Reith W, Recher M, Birchler T, Bassetti CL. Narcolepsy: autoimmunity, effector T cell activation due to infection, or T cell independent, major histocompatibility complex class II induced neuronal loss? Brain. 2010; 133(Pt 5):1300–1311. [PubMed: 20403960]
73. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet. 2007; 369(9560):499–511. [PubMed: 17292770]
74. Hor H, Kutalik Z, Dauvilliers Y, et al. Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy. Nat Genetics. 2010; 42(9):786–789. [PubMed: 20711174]
75. Vaarala O, Vuorela A, Partinen M, et al. Antigenic Differences between AS03 Adjuvanted Influenza A (H1N1) Pandemic Vaccines: Implications for Pandemrix-Associated Narcolepsy Risk. PLos ONE. 2014; 9(12):114361.
76. Julkunen I, Partinen M. Neuroimmunology: Disease mechanisms in narcolepsy remain elusive. Nat Rev Neurol. 2014; 10(11):616–617. [PubMed: 25311588]
77. Underwood EImmunology. Key narcolepsy-influenza vaccine findings retracted. Science. 2014; 345(6196):498. [PubMed: 25082675]
78. Ahmed SS, Schur PH, MacDonald NE, Steinman L. Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants. J Autoimmun. 2014; 50:1–11. [PubMed: 24559657]
79. Miller JD, Whitehair LH. Concurrent HLA-related response factors mediate recombinant hepatitis B vaccine major adverse events. Autoimmunity. 2005; 38(2):181–194. [PubMed: 16040339]
80. Hohler T, Meyer CU, Notghi A, et al. The influence of major histocompatibility complex class II genes and T-cell Vbeta repertoire on response to immunization with HBsAg. Hum Immunol. 1998; 59(4):212–218. [PubMed: 9568796]

81. Pan L, Zhang L, Zhang W, et al. A genome-wide association study identifies polymorphisms in the HLA-DR region associated with non-response to hepatitis B vaccination in Chinese Han populations. Hum Mol Genet. 2014; 23(8):2210–9. [PubMed: 24282030]
82. Poland GA, Ovsyannikova IG, Jacobson RM, et al. Identification of an association between HLA class II alleles and low antibody levels after measles immunization. Vaccine. 2001; 20(3–4):430–438. [PubMed: 11672906]
83. St Sauver JL, Ovsyannikova IG, Jacobson RM, et al. Associations between human leukocyte antigen homozygosity and antibody levels to measles vaccine. J Infect Dis. 2002; 185(11):1545–1549. [PubMed: 12023759]
84. Ovsyannikova IG, Jacobson RM, Dhiman N, Vierkant RA, Pankratz VS, Poland GA. Human leukocyte antigen and cytokine receptor gene polymorphisms associated with heterogeneous immune responses to mumps viral vaccine. Pediatrics. 2008; 121(5):e1091–e1099. [PubMed: 18450852]
85. Ovsyannikova IG, Jacobson RM, Vierkant RA, O'Byrne MM, Poland GA. Replication of rubella vaccine population genetic studies: validation of HLA genotype and humoral response associations. Vaccine. 2009; 27(49):6926–6931. [PubMed: 19761839]
86. Pajewski NM, Parker SD, Poland GA, et al. The role of HLA-DR-DQ haplotypes in variable antibody responses to anthrax vaccine adsorbed. Genes Immun. 2011; 12(6):457–465. [PubMed: 21368772]
87. Ovsyannikova IG, Pankratz VS, Vierkant RA, et al. Human leukocyte antigens and cellular immune responses to anthrax vaccine adsorbed. Infect Immun. 2013; 81(7):2584–2591. [PubMed: 23649091]
88. Lin Y, He Y. The ontology of genetic susceptibility factors (OGSF) and its application in modeling genetic susceptibility to vaccine adverse events. J Biomed Semantics. 2014; 5:19. [PubMed: 24963371]
89. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969; 89(4):422–434. [PubMed: 4305198]
90. Delgado MF, Coviello S, Monsalvo AC, et al. Lack of antibody affinity maturation due to poor Toll-like receptor stimulation leads to enhanced respiratory syncytial virus disease. Nat Med. 2009; 15(1):34–41. [PubMed: 19079256]
91. Graham BS. Biological challenges and technological opportunities for respiratory syncytial virus vaccine development. Immunol Rev. 2011; 239(1):149–166. [PubMed: 21198670]
92. Graham BS, Henderson GS, Tang YW, Lu X, Neuzil KM, Colley DG. Priming immunization determines T helper cytokine mRNA expression patterns in lungs of mice challenged with respiratory syncytial virus. J Immunol. 1993; 151:2032–2040. [PubMed: 8345194]
93. McLellan JS, Correia BE, Chen M, et al. Design and characterization of epitope-scaffold immunogens that present the motavizumab epitope from respiratory syncytial virus. J Mol Biol. 2011; 409(5):853–866. [PubMed: 21549714]
94. Correia BE, Bates JT, Loomis RJ, et al. Proof of principle for epitope-focused vaccine design. Nature. 2014; 507(7491):201–206. [PubMed: 24499818]
95. Cale CM, Klein NJ. The link between rotavirus vaccination and intussusception: implications for vaccine strategies. Gut. 2002; 50(1):11–12. [PubMed: 11772959]
96. Haber P, Patel M, Pan Y, et al. Intussusception after rotavirus vaccines reported to US VAERS, 2006–2012. Pediatrics. 2013; 131(6):1042–1049. [PubMed: 23669521]
97. Carlin JB, Macartney KK, Lee KJ, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. Clin Infect Dis. 2013; 7(10):1427–1434. [PubMed: 23964090]
98. Weintraub ES, Baggs J, Duffy J, et al. Risk of intussusception after monovalent rotavirus vaccination. N Engl J Med. 2014; 70(6):513–519. [PubMed: 24422678]
99. Klein SL, Pekosz A. Sex-based biology and the rational design of influenza vaccination strategies. J Infect Dis. 2014; 09(Suppl 3):114–119.

100. Beyer WE, Palache AM, Kerstens R, Masurel N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. Eur J Clin Microbiol Infect Dis. 1996; 15(1):65–70. [PubMed: 8641306]
101. Engler RJ, Nelson MR, Klote MM, et al. Half- vs full-dose trivalent inactivated influenza vaccine (2004–2005): age, dose, and sex effects on immune responses. Arch Intern Med. 2008; 168(22): 2405–2414. [PubMed: 19064822]
102. Weber SK, Schlagenhauf P. Childhood vaccination associated adverse events by sex: a literature review. Travel Med Infect Dis. 2014; 12(5):459–480. [PubMed: 24680600]
103. Shohat T, Manfred SG, Orly N, et al. Gender differences in the reactogenicity of measles-mumps-rubella vaccine. Isr Med Assoc J. 2000; 2:192–195. [PubMed: 10774264]
104. Benjamin CM, Chew GC, Silman AJ. Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine. Brit Med J. 1992; 304(6834):1075–1078. [PubMed: 1586818]
105. Khalil MK, Al-Mazrou YY, Al-Ghamdi YS, Tumsah S, Al-Jeffri M, Meshkhas A. Effect of gender on reporting of MMR adverse events in Saudi Arabia. East Mediterr Health J. 2003; 9(1–2):152–158. [PubMed: 15562745]
106. Lindsey NP, Schroeder BA, Miller ER, et al. Adverse event reports following yellow fever vaccination. Vaccine. 2008; 26(48):6077–6082. [PubMed: 18809449]
107. Pondo T, Rose CE Jr, Martin SW, et al. Evaluation of sex, race, body mass index and pre-vaccination serum progesterone levels and post-vaccination serum anti-anthrax protective immunoglobulin G on injection site adverse events following anthrax vaccine adsorbed (AVA) in the CDC AVA human clinical trial. Vaccine. 2014; 2(28):3548–3554. [PubMed: 24768633]
108. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis. 2010; 10(5):338–349. [PubMed: 20417416] ** This is a review that outlines the dfferences in vaccine immunogenicity and adverse events between the sexes.
109. Umlauf BJ, Haralambieva IH, Ovsyannikova IG, et al. Associations between demographic variables and multiple measles-specific innate and cell-mediated immune responses after measles vaccination. Viral Immunol. 2012; 25(1):29–36. [PubMed: 22239234]
110. Ovsyannikova IG, Jacobson RM, Vierkant RA, Jacobsen SJ, Pankratz VS, Poland GA. The contribution of HLA class I antigens in immune status following two doses of rubella vaccination. Hum Immunol. 2004; 65:1506–1515. [PubMed: 15603879]
111. Chen XQ, Bulbul M, de Gast GC, van Loon AM, Nalin DR, van Hattum J. Immunogenicity of two versus three injections of inactivated hepatitis A vaccine in adults. J Hepatol. 1997; 26(2): 260–264. [PubMed: 9059944]
112. Van der Wielen M, Van Damme P, Chlibek R, Smetana J, von Sonnenburg F. Hepatitis A/B vaccination of adults over 40 years old: comparison of three vaccine regimens and effect of influencing factors. Vaccine. 2006; 4(26):5509–5515. [PubMed: 16725234]
113. Bock HL, Kruppenbacher J, Sanger R, Hobel W, Clemens R, Jilg W. Immunogenicity of a recombinant hepatitis B vaccine in adults. Arch Intern Med. 1996; 156(19):2226–2231. [PubMed: 8885822]
114. Haralambieva IH, Ovsyannikova IG, Kennedy RB, Larrabee BR, Shane Pankratz V, Poland GA. Race and sex-based differences in cytokine immune responses to smallpox vaccine in healthy individuals. Hum Immunol. 2013; 74(10):1263–1266. [PubMed: 23806267]
115. Kennedy RB, Ovsyannikova IG, Pankratz VS, et al. Gender effects on humoral immune responses to smallpox vaccine. Vaccine. 2009; 27(25–26):3319–3323. [PubMed: 19200827]
116. Doria G, Frasca D. Genetic factors in immunity and aging. Vaccine. 2000; 18(16):1591–1595. [PubMed: 10689133]
117. Gardner EM, Gonzalez EW, Nogusa S, Murasko DM. Age-related changes in the immune response to influenza vaccination in a racially diverse, healthy elderly population. Vaccine. 2006; 24(10):1609–1614. [PubMed: 16260072]
118. Sukumaran, L.; Mcneil, MM.; Lewis, P.; Moro, P.; Shimabukuro, T. Adverse events following measles, mumps, and rubella (MMR) vaccine in adults reported to the Vaccine Adverse Events Reporting System, 2003–2013. San Diego, CA: ID Week meeting; 2014. Abstract 1077

119. Martin M, Weld LH, Tsai TF, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis. 2001; 7(6):945–951. [PubMed: 11747720]

120. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. RJ Infect Dis. 2009; 200(2):172–180.

121. Brighton Collaboration. [Date accessed, February 4, 2015] Immunize Safely. 2015. https://brightoncollaboration.org/public

122. World Health Organization. [Date accessed, February 4, 2015] Global Vaccine Safety Initiative. 2015. http://www.who.int/vaccine_safety/en/

Key Issues

- Adversomics is the application of immunogenomics and systems biology approaches to understand the genetic and non-genetic drivers of vaccine adverse reactions at the molecular level.
- Understanding and preventing serious adverse vaccine reactions is critical to improving public trust in vaccine safety and to developing new safe and effective vaccines.
- Vaccine immunogenicity and vaccine adverse events have been reported at higher rates for females than males for multiple vaccines; This observation warrants further evaluation.
- International partnerships between clinicians, public health officials, epidemiologists, and clinical, translational, and basic science researchers are needed to advance the field of adversomics.
- An international biobank of specimens from patients with vaccine adverse events needs to be created in order to conduct further adversomics studies.

Table 1

WHO Classification of Adverse Events Following Immunization.

WHO Classification of Causality [16]	Examples/Comments
A. Consistent causal association to immunization	
A1 and A2. Vaccine product-related and vaccine quality-defect related reactions	
• Reactions associated with site and route of administration	Local pain at injection site
• Immune-mediated vaccine reaction	
▪ Local	Injection site reaction
▪ Multisystem (generalized reactions)	Fever IgE mediated hypersensitivity Non-IgE mediated hypersensitivity Immune complex mediated reaction
▪ Organ-specific (may be autoimmune or undefined mechanism)	CNS (Guillain Barre syndrome)
• Reactions as a consequence of replication of vaccine-associated microbial agent	Yellow fever vaccine-associated viscerotropic/neurotropic disease
• Direct toxic effect of a vaccine component or metabolite	Product quality defect
A3. Immunization error-related reaction	
• Error in vaccine handling	Decreased efficacy due to maintenance of cold-chain
• Error in vaccine prescribing	Incorrect prescribing of a vaccine for which an individual has a known allergy to vaccine components
• Error in administration	Incorrect sterile technique resulting in a site infection
A4. Immunization anxiety-related reaction	Vasovagal and hyperventilation reactions
B. Indeterminate	
B1. Consistent temporal relationship but insufficient evidence for causality	The details of these cases should be noted in a national or international database. Over time, if similar cases are reported, the recorded cases may assist in identifying a signal that could suggest a causal association.
B2. Conflicting trends of consistency and inconsistency with causality	
C. Inconsistent causal association to immunization (coincidental)	
	Manifestation or complication of an underlying congenital, inherited, or acquired disease that may or may not have been diagnosed prior to immunization

Table 2

Vaccine Adverse Event Studies Utilizing Genetics or Components of Systems Biology

Vaccine Type	Adverse Event	N*	Study Design/Methods	Associations with Adverse Events	Reference
Childhood Immunizations					
DTaP, MMR,Hib	Vaccine-related seizures, epilepsy diagnosis after vaccination in children	23	Retrospective DNA sequencing of patients with events	65% cases had genetic or structural causes of seizures/epilepsy	Verbeek NE. Pediatrics 2014[40]
DTP, IPV, Hib	Vaccine-related seizures, epilepsy diagnosis after vaccination in children	14	Retrospective DNA sequencing of patients with events	100% cases had genetic or structural causes of seizures/epilepsy	Berkovic SF. Lancet Neurol 2006[41]
Vaccinations against Smallpox					
Aventis Pasteur Smallpox vaccine	Fever, generalized rash, lymphadenopathy	16; 24	Case-control Genotyping of SNPs	*MTHFR* *IRF1* genes	Reif DM. J Infect Dis 2008[44]
Dryvax	Fever, “acute Vaccinia syndrome”	94	Case-control Genotyping of SNPs	haplotypes in the *IL1* and *IL18* genes are associated with fever and variations in humoral immunity	Stanley SL, Jr. J Infect Dis 2007[53]
Yellow Fever Vaccine					
YF-17D	Viscerotropic disease	1	Descriptive case study Systems biology	Persistent viremia, robust induction of T and B cell responses, and polymorphisms in the chemokine receptor *CCR5* (delta 32) and its ligand *RANTES* (403G/A) genes	Pulendran B. J Infect Dis 2008[58]
YF-17D	Viscerotropic and Neurotropic disease	6	Descriptive case series; case control Cytokine profiling	RANTES, IL-6, IL-8, MIG (monokine induced by IFN-γ), GRO (growth-related oncogene), MCP-1 (monocyte chemotactic protein), TGF-β (transforming growth factor), and TNF-β (tumor necrosis factor)	Bae HG. J Infect Dis 2008[60]
Genetic Associations with Guillain-Barré Syndrome (not specific to vaccination)					
-	GBS	140	Case-control *TNF*-α genotyping	*TNF*-α 308 G/A and 857 C/T alleles	Prasad KN. Hum Immunol 2010[65]
-	GBS	120	Case-control *TLR4* genotyping	*TLR4* gene Asp299Gly and Thr399Ile mutations	Nyati KK. J Neuroimmunol 2010[66]
	GBS	9	Case-control *FcRL3* genotyping	*FcRL3* (Fc receptor like 3) gene (FcRL3-3-169C, FcRL3-6 intron3A, and FcRL3-8 exon15A)	Sang D. J Neuroimmunol 2012[67]
	GBS	263	Case-control SNP genotyping	*MMP9* (matrix metalloproteinase 9) gene (C-1562T)	Geleigns K. J Neuroimmunol 2007[68]

*N is for the number of vaccine adverse event cases studied

DTaP-diptheria-tetanus-acellular pertussis vaccine

MMR-measles, mumps, rubella vaccine

Hib-*Haemophilus influenza* type B vaccine

DTP-diptheria-tetanus- pertussis vaccine

IPV-inactivated polio vaccine

MTHFR- 5,10-methylenetetrahydrofolate reductase enzyme

IRF1- interferon regulatory factor-1

GBS-Guillain-Barré syndrome