Pediatr Infect Dis J. Author manuscript; available in PMC 2010 May 1.
Published in final edited form as:
Pediatr Infect Dis J. 2009 May; 28(5): 431–432.
doi: 10.1097/INF.0b013e3181a6a511
PMCID: PMC2843136
NIHMSID: NIHMS179348
PMID: 19395950

Adversomics: The Emerging Field of Vaccine Adverse Event Immunogenetics

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Vaccines have enabled tremendous decreases in infectious diseases, eradication of smallpox, saved lives, and remain among the most effective and cost-effective of our public health initiatives.[1] At the same time, as an ever larger number of vaccines are administered globally, increasing concerns about adverse events and reactions have been raised and threaten the public health successes attributable to vaccines. For example, the controversy surrounding measles-mumps-rubella (MMR) vaccine and thimerosal are emblematic of public concerns and perceptions regarding vaccine safety and vaccine adverse reactions (AEs). With current and future technologic advances such as high throughput whole-genome scanning, transcriptomics, epigenetics, proteomics, and new biostatistical approaches to understanding huge databases of information, we can better understand associations and mechanisms by which genetically-mediated individual variations in vaccine response and reactivity occur. Armed with such knowledge, the ability to predict such AEs, or to design new vaccine approaches that minimize or eliminate serious vaccine-related reactions could be devised, consistent with a more personalized or individual approach to vaccine practice which we have called adversomics (the immunogenetics and immunogenomics of vaccine adverse events at the individual and population level, respectively).

CURRENT KNOWLEDGE

Immune, inflammatory, idiosyncratic, and other responses to a vaccine are determined by a host of known and unknown factors, including individual characteristics (age, gender, race, medical condition, etc.), the quality and quantity of vaccine antigen(s), the number of doses administered, route of immunization, and host genetics. Although tremendous work has gone into understanding genetic susceptibility to infectious diseases,[2] attention now needs to turn toward understanding genetic susceptibility to vaccine-related AEs. Indeed in the case of live vaccines, one might simplistically envision administration of such vaccines as an "infection" and conceptually study the susceptibility to such reactions in the same manner.

To further develop this construct, we have hypothesized that adverse reactions and events may not be random, but may in fact be, in part, genetically predetermined. For example, early studies demonstrated that certain populations are unusually susceptible to measles vaccine reactions with post-vaccine febrile reactions among 11 different Amerind populations 0.4°C higher than in Caucasian populations.[3] It was speculated that genetic differences in Amerinds were associated with intensified reactions to measles vaccine. Studies of Native American children revealed higher risks for invasive *Haemophilus influenzae* type b infection than white children. Decreased IgG2 and IgG4 antibody responses to *H. influenzae* type b polysaccharide vaccine were observed in healthy Apache children, compared with white children, potentially explaining the higher incidence of *H. influenza* type b infections in Apache populations.[4] Later studies revealed specific Km and Gm genetic allotypes associated with poorer immune response.[5]

More recent studies have investigated the role of cytokines in the pathogenesis of AEs associated with live viral vaccines. A large study of AEs, including fever, lymphadenopathy, and localized or generalized rash, after smallpox immunization was associated with increased levels of IFN-γ, TNF-α, IL-2, IL-5, and IL-10, whereas individuals who did not report an AE demonstrated increased IFN-γ levels only during the acute phase compared with baseline levels after immunization.[6] Concerns regarding myopericarditis after smallpox vaccine has resulted in studies which are examining possible genetic associations.[7,8]

Additional insights into identification of genetic markers that affect immune and physiological responses to viral vaccines emerged from a study which examined the genetic basis for adverse events after smallpox vaccination.[9] The hypothesis was that subjects experiencing AEs exhibited unique genetic polymorphisms associated with AE reactions in response to smallpox vaccination. To test the hypothesis 346 smallpox (Dryvax) immunized individuals were genotyped for single-nucleotide polymorphisms (SNPs) in 19 candidate genes and assessed for the development of fever associated with the receipt of vaccine. This study showed that fever following smallpox vaccination was associated with specific haplotypes on the IL1 gene

complex, and in the IL18 and IL4 genes. Importantly, these findings raise the possibility that the same genetic polymorphisms linked to fever after smallpox vaccine may also influence fever risk after other live virus vaccines, including MMR.[9,10] For example, a small percentage of children who get vaccine-induced fever after MMR will develop febrile seizures. Knowledge of a genetic association could allow the development of predictive tests or preventive therapies that could be administered with vaccine to prevent such AEs.

In another study 131 healthy volunteers from 2 independent smallpox vaccine studies were genotyped across 386 genes and assessed for local and systemic AEs.[11] The authors reported that genetic polymorphisms in genes expressing an enzyme previously associated with adverse reactions to a variety of pharmacologic agents (ie, the methylenetetrahydrofolate reductase, MTHFR, gene) and an immunologic transcription factor (ie, the interferon regulatory factor-1, IRF1, gene) were associated with local and systemic AEs (an oral temperature >38.3°C, generalized skin eruptions, or enlarged or tender regional lymph nodes) after smallpox vaccination.

Our own laboratory has done extensive work in identifying genetic associations with HLA, cytokine, cytokine receptor, innate receptors, innate immune response genes, and signaling molecules and both humoral and cell-mediated immune responses.[12,13] This work has been fundamental to identifying and understanding associations between genetic polymorphisms and variations in immune responses. Such methods must now be turned toward understanding adverse events associated with vaccination. An example is that epidemiologic studies have quantified the risk of immune thrombocytopenic purpura (ITP) and anaphylaxis, attributable to the MMR vaccine in the second year of life as 1 case per 40,000 vaccinated children.[14,15] Recently France et al demonstrated that 76% of ITP cases in children ages 12 to 23 months were related to MMR vaccination.[15] Identification of a genetic association between MMR vaccine and ITP would be important and would inform attempts at developing preventive strategies or improved vaccines. A further example is the expanding recommendations for the use of seasonal influenza vaccine and the potential use of pandemic vaccines globally; studies of the genetic susceptibility to Guillain-Barre Syndrome (GBS) would be important.[16]

SUMMARY

We believe that adversomics (the immunogenetics and immunogenomics of vaccine adverse events at the individual and population level, respectively) is critical to understanding and preventing serious adverse vaccine-related events, developing the next generation of vaccines, and to improving public confidence in vaccine safety.

Significant difficulties in the growth of the field of vaccine immunogenetics include the difficulty of studying large enough numbers of subjects (rare AEs are, by definition, rare), lack of research funding, the complexity and extensive polymorphic nature of immune response genes, statistical issues of multiple comparisons and statistical power, issues of multigenic and other gene interactions such as complementation and epigenetic DNA modifications, and gender, racial, and ethnic differences. Nonetheless, the field of adversomics is growing due to scientific interest in understanding the basis for vaccine reactions, "push" from the growing field of individualized medicine, and consumer demand for safer vaccines. The capability to reproduce statistical associations in independent population-based studies remains essential to assessing the generalization of such studies. Clearly more comprehensive studies are needed to determine if there are associations between genetic variations among individuals and susceptibility to serious adverse events in response to vaccination. These factors combined with technologic ability will lead to a new era in vaccinology and better, safer vaccines.

Acknowledgments

Supported by the National Institutes of Health grants AI 33144, AI 48793, and AI 40065 for our vaccine immunogenetics studies.

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