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Application of the immunological disease continuum to study autoimmune and other inflammatory events after vaccination

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ABSTRACT

In vaccine safety monitoring, the evaluation of possible autoimmune events is challenging. Developing grouping systems based on pathophysiology, instead of organ systems, may enhance our ability to identify or verify associations between vaccines and adverse immunologically mediated events in clinical trials and post-licensure surveillance. Emerging data suggest that self-directed tissue inflammation occurs along a continuum from innate immune-driven diseases to adaptive immune-driven diseases. Herein, we develop this proposed classification for the vaccination setting in which inflammatory diseases are placed along a continuum according to the two major arms of the immune system, the innate immune arm (mediated by cells including neutrophils, macrophages and complement) and the adaptive immune arm (cell-mediated and humoral response). We incorporate hypersensitivity reactions and molecular mimicry vaccine-related reactions into this mechanistic scheme. We show how this could have important implications to assess mechanisms of potential immune-mediated adverse events following vaccination.

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1. Introduction

Rare, serious autoimmune and other immunologically mediated adverse events that follow vaccination are poorly understood and remain an area of evaluation and surveillance. Public concern and media coverage regarding immune-mediated adverse events can lead to decreased vaccine uptake and a subsequent fall in protective herd immunity [1]. To avoid misclassification, a strong need exists to correctly classify immune-mediated adverse events that follow immunizations. We propose a potential mechanistic classification of immune-mediated events for consideration as a research tool. This scheme is based on the immunological disease continuum model of inflammation against self which, rather than lumping inflammation against self exclusively under the “autoimmunity” umbrella, places the role of innate immunity on an equally important footing in the expression of human inflammatory disease [2]. We show how this classification system might permit more accurate evaluation of safety concerns for rare immune-mediated adverse events that may occur following vaccination, thus enhancing our ability to properly identify and

analyze associations in clinical trials and post-licensure surveillance.

2. Vaccine safety monitoring – the current status

Vaccines undergo safety evaluation in pre-marketing and post-marketing studies to identify vaccine-associated adverse events. Identification of adverse events of concern in clinical trials involves a combination of clinical and statistical approaches [3]. Typically, coding terms for adverse events are screened looking for unexpected associations between vaccine and adverse events with adverse event codes often combined into groups based on biological and clinical grounds [4]. Issues of concern are often further evaluated with post-marketing surveillance and controlled observational studies. Post-marketing evaluation of adverse events, including potential immune-mediated adverse events, reported to passive surveillance systems such as the US Vaccine Adverse Event Reporting System (VAERS), relies mainly on evaluating the post-vaccination temporal clustering and disproportionate reporting of clinical symptoms (e.g. that are potentially of immune origin such as ascending paralysis, or symptoms consistent with hyperthyroidism). In addition, reported rates of immune-mediated diseases after vaccination are compared to expected rates of disease [5–7]. Unexpected patterns in clinical or demographic characteristics are further evaluated in controlled observational studies and using principles of causality assessment [8] by taking into account

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Table 1

Aspects of vaccine development and delivery that could theoretically play a role in immune-mediated adverse events.

Adjuvant agents that activate the innate immune responses [96]
Adjuvant properties of the microbe itself, e.g. from nucleic acids or bacterial cell walls [46]
Pathogen activation of the immune system through molecular mimicry (e.g. GBS), epitope spreading, bystander activation, or polyclonal activation [15,71]
Preservatives or stabilizers used in the vaccine (such as gelatin) that may induce an aberrant inflammatory response through an unknown mechanism [97,98]
Components of culture medium in which vaccine is produced, e.g. anaphylaxis from vaccines grown in chick embryo cells [13]
Vaccine contamination at production or during injection that can lead to immunologic sequelae, such as contamination of vaccine by polymerases and other proteins [99], or microbial contamination during the injection process due to the unsafe disposal or reuse of needles [62]
Route of vaccine administration [16,19]

the magnitude and significance of the association, its consistency across studies and populations, and the biologic plausibility of an association between vaccine and adverse outcomes. Improving scientifically and mechanistically based classification systems for adverse events may contribute to a more reliable evaluation of potential associations between vaccines and immune-mediated diseases, including the classical autoimmune diseases.

Although only a few true associations have been found between vaccines and immunologically mediated diseases such as idiopathic thrombocytopenic purpura (ITP), Guillan Barre syndrome (GBS), and anaphylaxis [9–14], a wide array of post-vaccine immune-mediated adverse events has been reported. Most of them reflect only coincidental, temporal (not causal) associations, and can be related either to mild infections at the time of vaccination that are missed by parents and physicians or to other environmental triggers. Some may be normal immunological responses to foreign proteins rather than more serious aberrant reactions against self tissues. Also, anticipated immune responses could theoretically trigger disease in individuals with underlying predispositions. In theory, immune-mediated responses of inflammation against self could result from host responses to any component of the vaccine, including the immunogen, adjuvants, preservatives, or stabilizers, or be affected by the route of vaccine administration (Table 1). Host responses could be triggered by a variety of mechanisms, including molecular mimicry, epitope spreading, bystander activation, and polyclonal activation [15].

Another issue when considering possible immune-mediated vaccine adverse events is the route of administration. For example, BCG, when instilled into the bladder for the treatment of bladder cancer, has been associated with polyarthritis, oligoarthritis, conjunctivitis, and uveitis [16]. However, intradermal BCG vaccination has not been associated with immune-mediated sequelae except for possibly polyarthritis [16]. Anaphylaxis and allergic responses are also affected by the route of administration [17–19]. In addition, subjects experimentally immunized with influenza virus antigen in the joint space developed a stronger systemic antibody response than subjects immunized subcutaneously [19], although the relationship of the antibody response to the development of immune-mediated disease in this context has not been evaluated. In vaccine safety evaluation, immune-mediated diseases are typically considered as one large category or split into multiple smaller categories based on the affected organ system to increase the ability to detect possible associations. For example, immune-mediated adverse events might be grouped as “gastrointestinal autoimmune diseases,” “musculoskeletal autoimmune diseases,” and “neuroinflammatory autoimmune diseases” [20].

Mechanisms that underlie immune-mediated diseases (even those that affect the same organ system) can differ greatly and often are not organ-specific [2,21,22]. For example, “neuroinflammatory” events include both multiple sclerosis and acute disseminated encephalomyelitis, even though it is increasingly clear that these disorders develop by radically different immunopathogenic mechanisms [23–25]. System organ classification of immune-mediated adverse events for vaccine safety evaluation may result either in “false alarms” or in potential missed opportunities to detect meaningful associations.

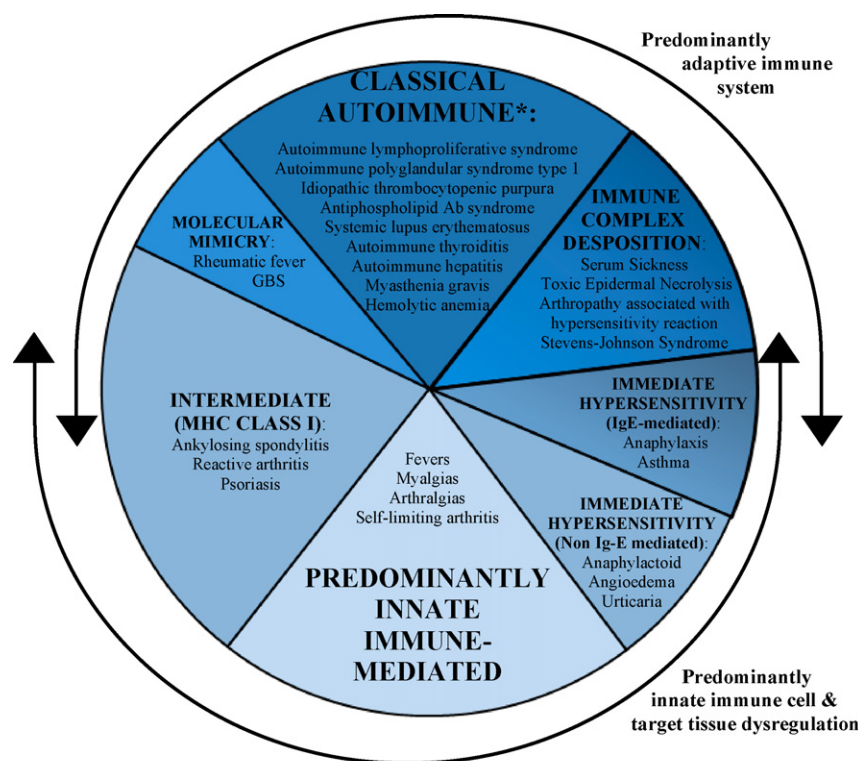
3. Recent advances in immune disease classification

Until recently, all “inflammation against self” was largely viewed as autoimmune. Likewise, our understanding of immune-mediated adverse events following immunization has been largely based on the same premise. The term “autoimmunity” has been used to designate inflammatory diseases related to aberrant adaptive immune responses with B cell or T cell directed reactivity against a self antigen [26]. However, an emerging network of genetic associations in common polygenic diseases underscores the key role of innate immunity (mediated by neutrophils, macrophages, and complement) in human diseases that were previously regarded as autoimmune [27–30]. There has also been an exponential increase in both knowledge of how innate immunity can fuel adaptive immunity [31], and how innate immune system dysfunction alone could be responsible for inflammation against self. The innate immune driven diseases have been collectively designated as autoinflammatory, in distinction from B and T cell driven autoimmunity [32]. We used the growing knowledge of the role of the innate immune system and immunologic mechanisms to develop a mechanistic classification system of autoimmune diseases [2]. Rather than simply designating all non-infectious inflammatory diseases against self as autoimmune, in this classification inflammatory diseases are placed along a continuum according to the two major arms of the immune system, the innate immune arm (mediated by cells including neutrophils, macrophages and complement) and the adaptive immune arm (cell-mediated and humoral response), with this scheme being underpinned by emerging human genetic studies [2].

The previously proposed immunologic disease continuum contains the classical autoimmune diseases, innate immune-mediated diseases, and “intermediate” diseases related to major histocompatibility complex (MHC) class I-associated disorders, and is well-reviewed elsewhere [21,33]. The classical autoimmune diseases (such as autoimmune thyroid disease, myasthenia gravis, and Sjogren’s syndrome) have been proposed to result largely from an aberrant response in primary immune tissue such as thymus and bone marrow, whereas the tissues under attack may be physiologically normal prior to disease onset [33]. These autoimmune diseases are typically mediated by MHC class II and manifest antibodies that are responsible for disease pathology [34]. In contrast, diseases primarily characterized by an aberrant innate immune activation at a specific location, due either to an intrinsic abnormality of the innate immune system or to tissue specific dysregulation leading to innate immune activation, represent the opposite to autoimmunity. As outlined below, many inflammatory conditions show a variable interaction between these extremes (Fig. 1).

4. A classification system of immunological events for vaccine surveillance, based on immune mechanisms

The present article groups immune-mediated adverse events following immunization based on the mechanistic classification of inflammation against self [2]. A major consideration with respect to this classification is that exogenous or foreign antigens, as



* Can cause induction of autoantibodies or induction of disease in patients

Fig. 1. Proposed immunologic disease continuum for use in vaccine safety surveillance. Classical adaptive immune-mediated diseases (where B and T lineage cells and the primary lymphoid organs are the chief protagonists in disease expression) are at one end of the spectrum and innate immune-mediated diseases (where the pattern of expression of innate immune related pathologies is critically dependent on tissue specific dysregulation of cells of the innate immune system or due to intrinsic defects in tissue barrier function, aberrant tissue repair, remodeling responses) are on the other side. Intermediate diseases (some of which have MHC class I associations) and IgE-related hypersensitivity are intermediates between classical autoimmunity and innate immune-driven diseases since there is a strong contribution from tissue specific factors in disease expression. The diseases and conditions contained in the figure are included for reference and do not represent a comprehensive list.

well as other components of a vaccine, may trigger the response. The resulting response may not necessarily be autoimmune, but may simply represent a “normal” inflammatory reaction against a foreign protein. We also include disease categories in these classification systems that are not “truly” autoimmune in nature because they represent important immunologic events that have been reported after vaccination. Such scenarios include IgE-mediated hypersensitivity diseases and immune complex deposition diseases, which may not be considered as truly autoimmune because they involve an interaction between an exogenous protein and the humoral arm of the adaptive immune response. We show how this classification system could be used to facilitate the evaluation of a full range of immunologically mediated events (including molecular mimicry, allergic reactions and immune complex deposition diseases) in vaccine safety analyses. This modified classification system is depicted in Fig. 1, and examples of immunologically mediated diseases in each of these categories are listed in Fig. 1; comprehensive categorization can be found elsewhere [2,21].

4.1. Classical autoimmune diseases in relationship to vaccine responses

Collectively, these conditions are associated with high-titer autoantibodies that predate clinical disease and typically demonstrate MHC class II associations. Indeed, high-titer autoantibodies may predate the clinical expression of diseases like rheumatoid arthritis, systemic lupus erythematosus, and type I diabetes mellitus by many years [35,36]. In relevant animal models, it is usually

necessary to use adjuvants to promote clinical expression of these autoimmune diseases, but the role of exogenous adjuvants in the development of classical autoimmune disease in humans is less well-defined [37,38].

Although there have been reports and epidemiological studies suggesting an association between measles-containing vaccines and the subsequent development of presumed autoantibody-associated idiopathic thrombocytopenic purpura [10,39], there are no specific studies demonstrating causal associations between other vaccinations and the onset of this category of autoimmune diseases. Studies that have examined the development of autoantibodies in healthy human subjects after vaccination failed to convincingly show a rise in autoantibody titers [38,40,41]. We are not aware of large epidemiologic studies in humans that have globally assessed the relationship between autoantibody titers and vaccines. In theory, this category of disease following immunization could be related to the non-specific effects of antigens or adjuvants triggering end organ damage in an already sensitized individual, although there is currently no compelling evidence for such a scenario following immunization.

Vaccination could nonspecifically activate the immune response, leading to an exacerbation of pre-existing autoimmunity rather than development of de novo disease [42]. It must be stressed that the exacerbation of a known autoimmune disease such as rheumatoid arthritis is usually transient and likely due to nonspecific stimulation of the innate immune response and is, therefore, not linked to disease causality as further set out below [43].

4.2. Innate immune-mediated reactions related to adjuvants

Adjuvants are often added to vaccines to enhance the immune response and limit the amount of inactivated viral or bacterial components needed [44]. Vaccine development faces the challenge of balancing the demonstrated benefits of adjuvants with potential harms. Understanding the molecular basis for innate immune-mediated adverse events following immunization and how they might relate to vaccine components continues to evolve and improve. The success of vaccination in mounting an adaptive immune response is critically dependent on the antigenicity of the vaccine. The first reaction that normally accompanies vaccination is an innate immune response, as it represents a nonspecific early response to a foreign antigen. Serious innate immune-mediated pathology following immunization is rare, as these reactions are typically benign and self-limited (e.g. fever, arthralgias and myalgias). However, some adjuvants tested in experimental settings, including lipopolysaccharide, have on occasion triggered a severe innate inflammatory response [45].

In addition to the exogenous adjuvants, inoculated bacteria or viruses have variable intrinsic adjuvant properties. Adjuvants that contain bacterial or viral components are thought to signal through toll-like receptors (TLRs) or an array of other pattern recognition receptors to trigger the innate immune system through dendritic cells and other antigen-presenting cells, which may result in specific adaptive immune responses [15,46]. It has been suggested that the adjuvant effect of these microbial pathogens could play a role in whether a triggered autoimmune response is benign and self-limited or severe and/or long-lasting [47]. Some TLRs (e.g. 1, 2, 4, 5) most commonly identify bacterial products, while others (e.g., TLR 3, 7, 9) sense nucleic acids [48,49]. Furthermore, different TLRs demonstrate varying tissue-specificity and may be found more commonly in some organs than others [50]. However, the clinical significance, if any, for adverse vaccine responses of differential TLR expression has not yet been determined.

The importance of different types of TLRs as potential drivers of self reactivity has been recently highlighted by the demonstration that TLRs 3, 7, 8, and 9 are essential for autoantibody development against nucleoproteins, which are the antigen targets for systemic lupus erythematosus and some other connective tissue diseases such as Sjogren's syndrome [51,52]. A better understanding of these pathways would be useful for understanding whether autoimmune and inflammatory adverse events might be triggered by adjuvanted vaccines [53]. Furthermore, the mechanisms through which non-bacterial or viral adjuvants trigger the innate immune system require further study [54].

4.3. Immune complex deposition diseases

Although immune complex diseases are more commonly reported after drugs such as antibiotics and monoclonal antibodies [55,56], they have also been reported after vaccines such as tetanus–diphtheria–pertussis [57] influenza vaccines [58], and rabies vaccines [59], and also following inactivated respiratory syncytial virus and measles vaccines that are no longer on the market [60]. Immune complex deposition diseases are type III hypersensitivity reactions, which occur when there are residual antibodies in the host due to previous sensitization [61]. Vaccines can lead to type III “Arthus” reactions when the sensitized host is injected with antigen on subsequent occasions (e.g. from a tetanus booster shot) and antigens deposited at the injection site are recognized by residual antibodies, resulting in local immune complex formation and subsequent injection site pain and swelling [62].

Antigen/antibody complexes can also be deposited more widely in tissues leading to serum sickness or hypersensitivity (leukocytoclastic) vasculitis. These reactions are not autoimmune *per*

se, although they represent an interplay between the adaptive immune system and the exogenous antigen. If vaccination-related, then these reactions should be self-limiting, and should clear if the antigen is fully degraded [63]. The persistence of these reactions in humans is seen in Henoch-Schonlein purpura, where the suspected driving antigen(s) is not clearly defined [64]. As shown in Fig. 1, immune complex deposition diseases have been designated as a separate category in the proposed classification system because they depend on the presence of exogenous antigens that leads to antigen/antibody complexes and disease. Given that this category of disease is critically dependent on Fc receptors, mast cells, and neutrophils, all components of innate immune responses, it is placed between classical autoimmunity and innate immune-driven disease [65,66].

4.4. Allergic reactions

Immediate hypersensitivity reactions include IgE-mediated and IgE-independent reactions, both of which lead to activation of mast cells and basophils that result in local and systemic release of vasoactive and inflammatory mediators [67,68]. Immediate hypersensitivity reactions are characterized by abrupt and sometimes severe presentations including urticaria, bronchospasm, angioedema, and anaphylaxis [68]. These reactions are due to an exogenous antigen (usually a component of the vaccine) and are therefore not truly autoimmune, but may represent either an adaptive immune response (IgE-mediated) or an innate immune response (IgE-independent, mediated by complement or by a direct toxic effect on mast cells). Again, due to the role of mast cells and basophils, and the recognition of barrier function perturbation with dysregulated innate immune responses in the hypersensitivity-related diseases, we have placed it as another type of intermediate between classical autoimmunity and innate immune driven disease [69].

4.5. Molecular mimicry as a mechanism of vaccine-induced autoimmunity

There are examples of post-infectious inflammatory reactions where specific antibody-mediated immunopathology or cell-mediated immunopathology, or both, are strongly suspected. Vaccines that contain microbial antigens could also induce autoimmunity through molecular mimicry [15,70–72]. The most striking example is Guillain-Barré syndrome (GBS) following campylobacter and other infections [73,74]. An association between GBS and the seasonal influenza vaccine was reported during the 1976–1977 “swine influenza” vaccination, but an association between GBS and subsequent seasonal influenza vaccines has not been confirmed [11,74].

Diseases like GBS, that may be associated with sequence similarities between foreign and self-peptides resulting in the cross-activation of autoreactive T or B cells by pathogen-derived peptides, are usually transient though recovery may be prolonged [75]. With natural clearance of the inciting agent by normal immune function or artificial clearance with antibiotics, these diseases do not become chronic (although initial severe end organ damage may lead to chronic disability). Classifying diseases in this category may be challenging due to our limited understanding of the antigens responsible for molecular mimicry, to the fact that antigenic mimicry is likely more complex than simple amino acid-sequence homology, and to our insufficient understanding of its importance in the development of autoimmune diseases [76,77]. Nonetheless, molecular mimicry retains an intrinsic appeal, because it links the current concepts of the role of the immune system in the host defense with the concepts of autoimmunity [76]. In theory, autoimmune reactions that occur as a result of molecular

mimicry may in fact represent a distinct mechanistic subgroup from other immunological diseases that may be clinically suspected by their generally self-limiting nature [78]. This is in contra-distinction to the classical autoimmune diseases where the triggering antigen, often an autoantigen, persists and tissue damage continues until the target organ is rendered functionless. For these reasons, and due to empirical observations of the generally favorable long-term outcomes of GBS reactions, we have designated “molecular mimicry” within a separate category of autoimmunity.

4.6. MHC class I-associated intermediate diseases – between innate and adaptive immunopathology

These diseases include a wide range of disorders that are collectively known as the seronegative spondyloarthropathies and include ankylosing spondylitis, psoriasis, Crohn's disease, ulcerative colitis, reactive arthritis, psoriatic arthritis and Behcet's disease. Some of these entities have MHC class I associations, including HLA-B27 in ankylosing spondylitis and reactive arthritis, HLA-Cw6 in psoriasis, and HLA-B51 in Behcet's disease. Unlike the classical autoantibody-associated autoimmune diseases, these diseases may be primarily due to the failure of immunological tolerance in the disease-prone sites [33,79]. Factors such as local trauma or infections at distant sites can lead to an aggravation of the inflammatory reaction at primary sites of disease.

An association with specific bacterial and viral triggering events has been described with these conditions. Published case reports have described the onset of Behcet's disease after vaccination with typhoid vaccine [80], and development of reactive arthritis after receiving tetanus, BCG, influenza and rabies vaccines [81–84]. However, none of these vaccines have been shown to be causally related to the onset of MHC class I related diseases.

4.7. Genetic predisposition

Given the emerging understanding of multiple genetic factors associated with autoimmune and innate immune driven disease, it is likely that vaccine responses may also be influenced by genetic factors [47,85]. Indeed, genetic polymorphisms (in methylenetetrahydrofolate reductase and immunological transcription factor 1) have been found to be associated with adverse events after smallpox vaccination [86]. Polymorphisms have also been hypothesized to be associated with adverse events after vaccination with BCG vaccine [87], and to be associated with autoimmune/innate immune syndromes or intermediates induced by adjuvants (ASIA) [47]. Although it remains unclear whether vaccines could be triggering events for autoimmune diseases in certain individuals, genetic markers are now being explored that could allow for an individualized assessment of these potential risks [88–90]. Much remains to be done to elucidate the role of genetics in predicting the immunologic response to vaccination. Advances in our understanding of human genetics have led to an improved ability to classify autoimmune diseases [2], and might also help explain some adverse vaccine reactions [77].

5. Discussion

A scientifically based system that allows for identification and evaluation of rare immune-mediated adverse events following immunization more fully in clinical trials, passive surveillance systems and controlled observational studies is critical. New vaccines, new adjuvants, new targeted vaccine recipient populations, and heightened public awareness will require continued improvements in the evaluation of immune-mediated adverse events following immunizations. To categorize diseases and obtain results that are

scientifically and clinically meaningful, a classification of immune-mediated adverse events based on pathogenesis, as the one we present here, is important.

In vaccine safety evaluation, it may be more enlightening to hypothesize that a vaccine component could cause or exacerbate specific immune-mediated diseases with a common mechanism, rather than identifying autoimmune reactions by organ system categories. Also, this scheme that is underpinned by the genetics of human inflammatory disease allows for an assessment of putative associations between vaccines and adverse reactions. For example, the emergent genetics of autism appear to relate it to intrinsic brain tissue dysfunction rather than to genes participating in either innate or adaptive immunity [91,92]. This knowledge permits a more rational mechanistic assessment for toxicity claims by allowing direct genetic comparisons of disease categories and does not support evidence of a direct immune-mediated reaction in the case of autism, although the possibility of direct cellular toxicity (non-immune factors) cannot be fully excluded [91,92].

After licensure, vaccine safety is monitored by several methods: the Vaccine Adverse Events Reporting System (a nationwide passive surveillance system managed jointly by the FDA and the CDC), the Vaccine Safety Datalink (an analytical monitoring system managed by the CDC), other methods sponsored either by federal government agencies such as the FDA and CDC, or by vaccine manufacturers (e.g. FDA-required Phase 4 studies) [7,93,94]. The classification system described here could become a useful tool for the categorization of autoimmune diseases for studies conducted in any of these databases. Reaching consensus regarding the most valid approach for the investigation of autoimmune vaccine adverse events is essential to improve the capacity to compare and validate epidemiological studies of autoimmune diseases following vaccination in different settings.

As introduced earlier, a limitation of the evaluation of immune-mediated adverse events in controlled studies is that often studies are not large enough to fully evaluate such rare adverse events. Organ class groupings have been used with MedDRA coding to increase the number of adverse events available for comparison. When such groupings mix adverse events of different underlying immune mechanisms, the ability to detect true associations may be diminished because such non-differential misclassification can lead to reduction in the observed relative risk between the exposed and control group [95]. The categorization of different types of immune-mediated adverse events following immunization using the classification outlined in this paper might be done at several levels. When only MedDRA codes are available, a mapping between those codes and the appropriate disease category will need to be made. If additional information from medical records can be obtained, the classification can be based on the clinical history and examination findings, supplemented with inflammatory markers, autoantibodies and other tests to better delineate specific mechanism categories. Methods for automated extraction of such information from electronic records should help make this approach become more widely available. Pre-specified analyses based on hypotheses of theoretical associations between vaccine components and immune-mediated adverse events of a certain type could be conducted, along with more general screening analyses to identify possible safety concerns, depending on the stage of development and available data sources.

This classification system is limited by our current scientific understanding of immunologic principles that underlie immune-mediated diseases. In addition, there may be significant overlap between categories since autoimmune and inflammatory diseases truly lie on a spectrum; as such, categories may be difficult to fully separate in statistical analyses. Evaluation of this proposed approach is needed to assess its utility and value before widespread adoption can be recommended. This system represents a first

exploratory step towards a more accurate classification system for evaluating potential associations between vaccines and rare immune-mediated adverse events. While we seek to continuously improve the vaccine safety evaluation and monitoring system, review of existing information about immune-mediated adverse events following immunization in the context of this mechanistic classification system using the immunological disease continuum model as proposed in this article suggests that, with respect to the precipitation of chronic inflammation reactions against self, vaccines on the whole appear to be remarkably safe.

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