The Pathophysiology of Arthritis Due to Viruses and Vaccines

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Andreas M. Reimold

Abbreviations

ACPA	anticitrullinated protein antibody
APL	antiphospholipid
ASIA syndrome	Autoimmune/inflammatory syndrome induced by adjuvants
CCP	cyclic citrullinated protein
CMV	cytomegalovirus
EBV	Epstein-Barr virus
ENA	extractable nuclear antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
HTLV-1	human T cell leukemia virus-1
IFN	interferon
ISG	interferon-stimulated genes
MHC	major histocompatibility complex
sAg	surface antigen
β2GP1	beta-2 glycoprotein-1

Viruses Causing Arthralgias or Arthritis

At least 219 viral species are known to infect humans and increasingly sensitive methods in describing the human virome will likely describe orders of magnitude higher numbers of viruses that colonize and possibly infect humans [1]. A viral infection is an extremely common cause of joint symptoms, especially arthralgias (Table 9.1). Viruses generally affect all age groups. The main routes of infection are airborne, person-to-person, and occasionally via fomites. Once in the body, viruses spread widely during viremia but can also be distributed to specific sites through immune complexes or by trafficking within specific cell types.

Susceptibility to arthritis is influenced by host factors: age, genetics (susceptibility to outsize inflammatory or autoimmune reactions), gender, presence of comorbidities, and health status of joint tissues [2, 3]. In addition, viral factors also influence the likelihood of joint involvement: virulence of the virus, ability to produce toxins, degradability of viral products, and tissue tropism to joints.

Host factors affecting risk of bacterial septic arthritis are more numerous than those recognized for viral arthritides. For example, local factors predisposing to bacterial infection such as direct joint trauma, joint surgery or open reduction of fractures, arthroscopy, intraarticular injection, and prosthetic joint implants are not prominent in the pathogenesis of viral arthritis. However, host factors that affect a robust immune response are relevant to both bacterial and viral infections: extremes of age, use of biologics and immunosuppressant drugs, and comorbidities such as renal failure, malignancy, and diabetes mellitus. Finally, social factors are important for susceptibility to viral infection in terms of overall health such as low socioeconomic status or chronic alcohol abuse, or for specific exposures such as risky sexual behavior or intravenous drug abuse [4].

Mechanisms of Viral Infections

Innate Immune Responses

Multiple mechanisms must be considered to explain the joint features of viruses. Acute viral infection has systemic effects without direct invasion of the joints in most cases. Release of cytokines such as IL-1 and IL-6 is part of the febrile response that includes arthralgias. The first line of defense is the innate immune system [5].

A. M. Reimold (✉)
Internal Medicine, Rheumatic Diseases Division, Dallas VA Medical Center and University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: andreas.reimold@va.gov

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_9

Table 9.1 Viruses that cause articular symptoms

	Arthralgia/arthritis	Maximum duration	Synovial invasion
Parvovirus B19	60% of adults	Months, and rare recurrences	
Rubella virus and rubella vaccine	30% of women	2 weeks, rarely up to a year	Yes, also immune complexes
Alphaviruses (e.g., Chikungunya)	Arthralgia/arthritis in 100%, chronic arthritis in Chikungunya	Mostly 3–6 months, rarely >3 years	Virus persists in synovial macrophages
Ebola virus	Arthralgia common, synovitis 14%	63% after 9 months	Likely
Ebola vaccine rVSV-ZEBOV	Arthritis/arthralgia in 22%	Usual 18 days, occasionally months	Yes [124]
Flaviviruses:			
Dengue	Arthralgia 80%		
Zika	Arthralgia common, no arthritis	Usually 7 days	
Mumps	Arthritis is rare	Few weeks	
Enteroviruses: (Coxsackievirus, Echovirus)	Arthritis is rare	Most days to weeks, rarely up to months	Echovirus occasionally isolated from joints
Adenovirus	Arthritis is rare	Self-limited	
Herpes viruses:			
Varicella-zoster virus	Arthritis is rare	Self-limited	Occasionally isolated from joint Virus is latent in B cells
Epstein–Barr virus	Rare, large joint arthritis	Self-limited	
Herpes simplex virus	Rare, arthritis during generalized HSV-1 infection	Self-limited in <3 months	
Cytomegalovirus	Rare, arthritis in the immunosuppressed	Months	
Hepatitis A	Arthritis is rare	Usually self-limited, rarely chronic, relapsing with associated vasculitis	
Hepatitis B	Arthritis in up to 25%	Self-limited, never chronic arthritis	Immune complex formation
Hepatitis C	Arthralgias common Arthritis in up to 20%	Long-term oligoarthritis or RA-like arthritis	Immune complex formation with mixed essential cryoglobulinemia
Hepatitis E	Arthralgia		Cryoglobulinemia [125]
HIV	Painful articular syndrome, rare progression to arthritis	24 hours	
	Reactive arthritis	Chronic, relapsing	
	Psoriatic arthritis	Chronic	
	Diffuse infiltrative lymphocytosis syndrome (DILS)	Chronic sicca symptoms	
	Immune reconstitution inflammatory syndrome	May include RA-like symptoms	
HTLV-1	Chronic medium- and large joint arthritis [126]		

Data from Moore TL and Syed R. Specific viruses that cause arthritis. UpToDate 08-07-2018

1. *Pattern recognition receptors* (*PRRs*): PRRs such as retinoic acid inducible gene 1 (RIG-1), melanoma differentiation-associated gene 5 (MDA-5), and toll-like receptors (TLR-s) are expressed by leukocytes, epithelial cells, fibroblasts, and brain cells to initiate signaling pathways that converge at the activation of transcription factors (interferon [IFN]-regulatory factor 3 and IRF 7, NF-κB) to upregulate type I IFNs.
2. *Type I interferons*: Interferons binding to receptor (IFNAR) then lead to expression of multiple IFN-stimulated genes (ISGs), proinflammatory cytokines, and chemokines. ISGs include oligoadenylate synthetase (OAS), ribonuclease L (RNaseL), IFN-inducible dsRNA-dependent protein kinase (PKR), and myxovirus resistance (Mx) protein that are all involved in antiviral effects on different aspects of a virus' life cycle. ISGs are additionally simulated by other innate pathways (double-stranded RNA, single-stranded RNA) and feedback loops related to IFN signal signaling proteins.
3. *Apoptotic pathways*: Apoptotic pathways are also upregulated by innate immune system activation. The intrinsic apoptosis pathway is initiated by the release of cytochrome C from mitochondria and results in a cascade leading to the effector caspase-3. The extrinsic apoptotic pathway is mobilized by TNFα, TRAIL or FASL and leads to the death pathway involving FADD and Caspase 8. Some viruses produce antiapoptotic proteins such as IAP and Bcl2, and CHIKV hides in apoptotic blebs,

which are taken up my macrophages without an inflammatory response.

After viral infection, there is a rapid induction of type I interferon (IFNα and IFNβ) and the production of proinflammatory cytokines by resident cells. An acute viral infection that is contained and then eliminated by the host is a common pattern of infection. Examples are rhinovirus and influenza virus, which as a rule do not result in chronic or latent infections.

Adaptive Immune Responses

Up to 90% of viral pentapeptides are shared by the human proteome, making it likely that these sequences usually do not elicit an immune response due to tolerogenic mechanisms. However, in the setting of impaired tolerance or a break in tolerance produced by a vaccine adjuvant, exposure to these viruses makes the possibility of autoimmunity more likely [6, 7].

The adaptive immune system has an important role in the pathogenesis of joint symptoms and is a key part of the body's response to all arthritogenic viruses. The humoral immune response first produces IgM antibodies in the acute phase, then undergoes class switching to IgG antibodies, which, when neutralizing, can help to clear the virus and prevent reinfection in many cases. IgG responses can occur within days of the first IgM responses, can be neutralizing, and therefore can be markers of a robust and successful humoral immune response. Persistence of an IgM response has correlated with persistent Chikungunya virus (CHIKV) infection and prominent joint symptoms while later recurrence of an IgM response can signal reinfection or reactivation of the virus [8].

The cellular immune response to viruses consists of a rapid mobilization of CD4+ and CD8+ T cells. CD4+ responses can skew toward Th1 and produce cytokines such as TNFα, IL-1b, IFN-γ, and IL-12 while Th2 and Th17 responses produce cytokines such as IL-4, IL-13, and IL-17. The activation of CD8+ T cells is the classic immune response of cytotoxic cells that attack infected cells presenting viral antigens in conjunction with MHC Class I on their surface. Rapid clonal expansion of antigen-specific T cells and the acquisition of effector functions (providing T cell help or generating T cytotoxic capability) occur after viral infection and lead to rapid clearing of the virus in most cases. After the initial immune phase, the T cells have a contraction phase where most responding cells are eliminated while a small number of memory T cells survive long term and are available to respond to future reinfections. One example is the rapid CD8+ T cell responses to CHIKV, which has been associated with production of IL-4, IL-10, and IFN-γ [9].

Latent and Chronic Viral Infections

Latent infection can be defined clinically as viral infection without viral replication, but without viral eradication. After an acute primary infection, the period of viral latency may be punctuated by clinical or subclinical relapses. A latent, occult, noninfectious form of the virus can be due to an integrated genome or as episomal nucleic acid. Immunologic mechanisms of viral latency may include: (1) evasion of a cell-mediated immune response, e.g., by down-regulation of MHC class I molecules so that T cell (CTL and NK) recognition is lost; humoral antibodies may cap viral antigens on the cell and cause them to shed (e.g. measles/SSPE), leaving the host cell surface without viral proteins and (2) infection of immunoprivileged sites such as the brain.

Episomal latency refers to viruses maintaining their nucleic acid separately from that of the host cell, usually in the cytoplasm. Advantages of episomal latency are that the cytoplasmic virus may not enter the nucleus, avoiding the nuclear bodies called nuclear domain 10 (ND10) that restrict viral gene expression [10]. Disadvantages to episomal latency include increased exposure to cellular defenses and degrading enzymes. Examples of viruses using this strategy are HSV-1, HSV-2, and VZV in sensory ganglia and brain; CMV in lymphocytes, macrophages, and myeloid progenitor cells; and EBV in B lymphocytes [11].

In proviral latency, the viruses' genome is integrated into the host's DNA. Advantages for the virus include that host cell division leads to viral replication and that removing the virus without killing the host cell is not possible using current technology. Disadvantages are that the virus needs to enter the cell's nucleus, requiring packaging proteins that allow for this step. HIV is an example for proviral latency [12].

A persistent or chronic viral infection refers to a continuously replicating virus that remains infectious but that may or may not cause ongoing clinical symptoms. With a chronic persistent (replicative) infection, the essential functions of the host cell may be largely intact (e.g., DNA and RNA synthesis, protein synthesis). Examples include HIV infection, most cases of hepatitis C virus infection, and certain adult cases of hepatitis B infection [13].

Viruses that demonstrate latent infection also have the potential for lytic replication (Table 9.2). One example is parvovirus B19 that persists in blood and bone marrow of immunocompromised patients (chemotherapy, HIV, congenital immunodeficiencies, transplants) and is commonly harbored in human skin, making it difficult to ascribe causality for skin lesions by PCR rather than clinical means [12, 14]. Parvovirus B19 maintains latency by regulating inflammatory pathways that include AP-1, SP1, NF-κB pathway, TNFα, and p53 through virus-encoded NS1 protein [15]. Two mechanisms have been proposed for viral reactivation of herpesviruses (e.g., HHV6, HHV7, EBV, CMV) and par-

Table 9.2 Potentially arthritogenic viruses showing lytic as well as latent infection

	Clinical conditions
Herpesviridae	
HSV-1	Cold sores, encephalitis, pharyngitis, keratitis, whitlow
HSV-2	Genital herpes
VZV	Chicken pox, shingles
EBV	Mononucleosis, lymphoma (Burkitt's, NHL), nasopharyngeal ca
CMV	Congenital effects, mononucleosis
Parvoviridae	
Parvovirus B19	Fifth disease, gloves-and-socks syndrome Children: large joint oligoarthritis; adults: RA-like pattern of arthritis
Others	
HIV	HIV-associated arthritis Painful articular syndrome Reactive arthritis, psoriatic arthritis, USpA Rheumatoid arthritis Immune reconstitution inflammatory syndrome
Hepatitis B	Hepatitis, RA-like joint pattern of arthritis
Hepatitis C	Hepatitis, RA-like pattern of arthritis Vasculitis, sicca syndrome, arthralgias/arthritis, and fibromyalgia Cryoglobulinemia: large joint nonerosive oligoarthritis (e.g., at ankles)
HTLV-1	Chronic large and medium joint oligoarthritis. Associated eye, skin, muscle disorders

Data from Traylen et al. [127]

voviruses: (1) a stimulus elicits a potent immune response with a cytokine storm, resulting in viral reactivation; and (2) a stimulus may cause relative immunosuppression (hypogammaglobulinemia, reduced B cell count, and activation of monocytes and T cells) that leads to viral reactivation [16]. The exact virus-encoded proteins involved in triggering viral reactivation are not well understood in many cases. Speculation about the mechanisms has included major gene rearrangements as well as alteration of nucleotide sequences in transcription machinery binding sites, leading to a switch from latent to lytic infection [17].

The listing of acute, latent, and persistent viral infections does not always correlate well with observed clinical patterns. For example, parvovirus B19 is clinically an acute infection without chronicity in immunocompetent hosts, yet viral sequences may remain detectable by molecular techniques in the bone marrow. Nonreplicating parvovirus B19 DNA has been readily demonstrated in bone marrow of healthy controls as well as in 7 of 22 (32%) rheumatoid arthritis patients [18]. However, features of RA did not correlate with the presence of parvovirus B19. At the same time, persistence of parvovirus in the setting of additional mutations in the immune system can lead to further insights into immune functioning. One recent example was a chronic parvovirus infection in a patient with a novel mutation in the ELANE (neutrophil elastase) gene [19]. This patient had decreased neutrophil NET (neutrophil extracellular trap) formation and decreased IL-8 and IL-12 production resulting in decreased neutrophil chemotaxis and antiviral immunity. The patient experienced daily fevers, rash, and inflammatory arthritis with chronic parvovirus infection.

Mechanisms of Chronic Arthritogenic Viral Infection

Certain viruses can cause a chronic infection, some directly in joint structures and others elsewhere in the body. Examples include HIV, hepatitis B and C, EBV, and CHIKV. The initial host antiviral response results in elaboration of IL-10 and type I interferons, which provide immunosuppressive signals that are essential for viral persistence. On the other hand, gp130-dependent cytokines such as IL-6, IL-11, and IL-27 continuously support proinflammatory responses of the humoral and cellular immune systems. Common gamma-chain cytokines IL-2, IL-7, and IL-21 help to maintain the viability and function of the T cell pool and their levels can be modulated to optimize immune responses and achieve viral clearance. The complexity of the system is further reinforced by observations of diametrically opposite immune effects by certain cytokines in different circumstances. One example is the effects of type I interferon on the clearance of lymphocytic choriomeningitis virus (LCMV) virus in a mouse model, which enhances clearance for chronic strain Cl-13 while decreasing clearance for lymphocytic choriomeningitis virus–Armstrong (LCMV-ARM) strain [20].

In chronic viral infection, an ongoing potent immune response may not be desirable due to the potential for causing host damage from uncontrolled T cell expansion. On the other hand, a muted immune response reduces immune surveillance and permits viral persistence. During chronic viral infection, immune exhaustion can occur by which both CD4+ and CD8+ T cells lose their main effector functions [21]. Exhausted CD4+ cells lose most of their production of effector cytokines such as IL-2, TNFα, and IFN-γ, have increased expression of inhibitory cell-surface receptors such as PD-1 and CTLA4, and increased production of IL-10 and IL-21. Exhausted CD8+ T cells have increased expression of inhibitory receptors PD1, LAG-3, 2B4, Tim3, and CD160, with decreased cytokine elaboration, decreased proliferation, and decreased cytotoxic activity. Over time, the population of effector T cells dwindles and the antiviral response also decreases. Further research efforts are underway to manipulate cytokine levels in order to limit or reverse T cell exhaustion.

Chikungunya virus, an alphavirus, is a rare example of a virus causing recurrent arthralgias or even polyarthritis up to 3 years after initial infection [22]. Indeed, CHIKV has been demonstrated to set up a chronic infection with tropism for

synovial tissues such as synovial macrophages and osteoblasts [23]. Virus persists intracellularly, thus evading immunosurveillance and allowing viral persistence. At the same time, infection of macrophages/monocytes and other immune system cells leads to chemokine and cytokine production and inflammatory cell recruitment, all resulting in clinical swelling and pain at the joints.

Ebola, another alphavirus, is also known to cause chronic arthralgias and persistent arthritis, sometimes for years after initial infection. For Ebola, the most frequent symptom of survivors is asymmetric arthralgias. For example, in a group of 44 survivors reporting arthralgias with their initial infection, 63% had musculoskeletal pain 9 months after discharge, of which 14% had synovitis on examination [24].

Immune complex deposition is a further mechanism by which certain viruses cause joint symptoms. For example, hepatitis B virus can lead to immune complex formation followed by deposition in synovial tissue, and hepatitis C virus can result in immune complex deposition leading to mixed cryoglobulinemia [11].

Mechanisms That Allow Autoimmunity

A genetic component underlies all of autoimmunity. Most autoimmune arthritic diseases have been associated with genetic susceptibility loci, especially in the MHC class I and class II loci. As one common example, it has been found that the HLA-DRB1 loci are associated with at least 30 autoimmune conditions [25]. These genetic loci are associated with tailored and possibly an overactive immune response, so that individuals with these loci produce more autoantibodies even without the presence of overt disease. It has been proposed that breakdown of immune tolerance occurs especially in those individuals with aberrant presentation of antigen on MHC class II to autoreactive T cells. Such a mechanism of broad reactivity may persist over generations if it provides a survival advantage by allowing the clearance of an infectious organism that otherwise evades the immune system [26].

Molecular Mimicry

Autoreactivity through molecular mimicry is often the most important mechanism of autoimmunity in viral infections. In this scenario, self-proteins would bear stretches of identity or a high percentage of similarity to viral sequences. With the break in tolerance caused by the virus (or by a vaccine and its adjuvant), an immune response becomes possible against both the viral sequences and the similar or identical self-protein sequences. In one experiment, over 600 monoclonal antibodies were made against 11 viral proteins and tested for reactivity with 14 mouse organs [27]. The results showed that an antivirus monoclonal had crossreactivity against host tissues in 3.5% of cases, making molecular mimicry a common phenomenon in humoral immune responses.

In addition, molecular mimicry has been demonstrated in the T-cell responses of cellular immunity [28]. Homology was found between the protein sequence in the polymerase gene of hepatitis B virus and myelin basic protein (MBP), a key target in the animal model of multiple sclerosis, experimental autoimmune/allergic encephalomyelitis (EAE). Injection of the viral sequence into animals indeed caused T cell reactivity and an EAE-like disease [29]. In a separate work, in vitro studies of autoreactive T cell clones directed at MBP could be activated with viral peptides [30]. While the presentation of antigen to autoreactive T cells by APCs in conjunction with MHC class II and simultaneous crossreactivity with viral sequences are not uncommon phenomena, it has been proposed that not all such interactions lead to florid autoimmune disease. It is likely that only when the viral sequence mimics a particularly potent disease-inducing self-epitope does the full-blown autoimmune disease develop. In most other cases, the self-reactivity and crossreactivity do not progress to clinical symptoms [31]. Theories of molecular mimicry in the etiology of autoimmune and rheumatic diseases have been advanced in spondyloarthritis, antiphospholipid syndrome, rheumatoid arthritis, and systemic lupus, among others [32–35].

Bystander Activation

Bystander activation is a further mechanism causing an autoimmune response to virus infection or to vaccination [31]. Three pathways can be envisioned. First, a viral infection can lead to the activation of potent antigen-presenting cells such as dendritic cells. Both appropriate antigen presentation and the release of cytokines by APCs could activate self-reactive T cell clones and lead to autoimmune manifestations. Secondly, virus-specific CD8+ cytotoxic T cells will traffic to sites of virally infected cells where they will lyse the cells. The milieu of dying and infected cells will attract multiple inflammatory cells such as macrophages and T cells, causing release of cytokines such as TNFα and lymphotoxin [36]. This cytokine release can lead to bystander killing of uninfected cells. Thirdly, a similar mechanism of inflammatory cytokine release by CD4+ T cells has been proposed to result in further bystander killing [37].

Polyclonal Activation and Superantigens

HCV is an example of a virus that can act as a polyclonal activator on specific B and T lymphocyte populations [38]. Such polyclonal stimulation results in enhanced antigen pro-

cessing and the presentation of self-antigens, setting the stage for an autoimmune response. In addition, it was found that chronic HCV infection disrupts the tolerance mechanism that normally deletes autoreactive B cells, therefore increasing the risk of developing autoimmune antibodies. A related effect is seen with viral or virus-induced superantigens, which activate large numbers of polyclonal T cells that express particular Vb gene segments of which some could be specific for a self-antigen [39]. A massive cytokine release results. Of the viruses considered in this chapter, superantigens can be part of infection by CMV, EBV, and HIV.

Epitope Spreading

Epitope spreading refers to expansion of the immune response to target not just the initial epitope but also additional epitopes over time [40]. This mechanism was demonstrated in an animal model using Theiler's virus infection of the central nervous system and leading to recognition of host myelin epitopes [41]. Key factors in autoimmunity induction were a virus that induced Th1 immunity, the host's genetic background, and chronic viral infection.

Cytokines and Chemokines

Chemokines signal inflammatory cell trafficking into sites of inflammation while cytokines are key effectors of pro- and antiinflammatory responses. Cytokine effects include shaping of the T helper cell pathways such as Th1, Th2, and Th17. Viruses causing arthritis may cause local damage by high-level cytokine release in the host at times through transactivation of the host cytokine gene by viral products. One example is the transactivation of the proinflammatory IL-6 promoter by the NS1 protein of parvovirus B19, leading to high IL-6 cytokine levels and making it a key component of the host's inflammatory response to infection [42]. The complex relationship between viruses and cytokine levels is further highlighted by the actions of human papillomavirus, which inhibit the actions of proinflammatory JAK/STAT transcription factors and yet activate STAT-5 with downstream activation of the ATM and ATR DNA damage response pathways, resulting in HPB genome amplification [43].

Viruses as Protection Against Autoimmunity

There is a flip side to the commonly discussed induction of autoimmunity by viral infections, namely a protective effect of certain viral infections against the development of autoimmunity. Some examples include the decreased rate of type 1 diabetes in those with Group B Coxsackievirus, EBV infection, or LCMV infection [44]. Several mechanisms have been proposed [31]: (1) inducing apoptosis of autoreactive cells, (2) influencing cellular trafficking of autoreactive cells away from target organs, or (3) immune suppression and production of antiinflammatory cytokines (IL-10, TGFβ).

One line of inquiry has raised the possibility that HBV infection protects against the development of SLE. Studies in Colombian and Chinese populations with relatively high rates of endemic HBV demonstrated that hepatitis B infection occurred at lower rates in their SLE patients than in the general population [45, 46]. In Colombians, 2.5% of 117 SLE patients versus 10.7% of healthy controls had anti-HBc antibodies while in the Chinese cohort, 2.33% of SLE patients versus 9.57% of the general population had HBsAg. Any potential mechanism for protection against autoimmune disease by HBV infection awaits further investigation.

Overall, a definite causative or protective effect for viruses in autoimmune disease has been difficult to demonstrate. Humans have multiple chronic or remote viral infections, and most have been cleared at the time of autoimmune disease onset. The genetic background and environmental exposures are additional factors influencing autoimmunity.

Common Rheumatologic Syndromes Associated with Viral Infections

Sjögren's Syndrome

Sialotropism is a feature of several viruses and has led to an association with Sjögren's syndrome. For example, hepatitis C virus and HIV are both recognized as causing sialadenitis, sicca symptoms, and distinctive autoantibody production. Because of these associations, the classification criteria for primary Sjögren's syndrome require that HCV and HIV are ruled out as etiologies. Previous studies have also detected Epstein–Barr Virus (EBV), Coxsackie virus, and human T-lymphotropic virus (HTLV-1) in salivary gland tissue of Sjögren's patients without providing conclusive evidence of causality for the syndrome [47–51]. Besides infection of CD4+ T cells, HTLV-1 was shown to infect salivary gland epithelial cells and result in the upregulation of molecules involved in cell adhesion, inflammation, and migration [52]. In addition, a recent report added hepatitis delta virus detection in half of the samples tested from 15 primary Sjögren's syndrome patients [53]. In a mouse model, expression of hepatitis D virus antigens in salivary tissue recapitulated the pathologic features of Sjögren's syndrome including autoantibody formation, reduced salivary flow, and the formation of lymphocytic foci. Previous animal studies using in vivo expression of proteins from hepatitis C virus or HTLV-1 recapitulated incomplete Sjögren's features, most notably lacking induction of SSA or SSB [54, 55]. Therefore, it may

be that only specific viruses are associated with the full range of Sjögren's syndrome while others lack specificity.

Vasculitis: Giant Cell Arteritis

Herpes zoster has been investigated as a cause or trigger of giant cell arteritis based on both histopathologic and epidemiologic studies [56]. Varicella-zoster virus induces a T cell–mediated immune response, causes vascular changes such as multinucleated giant cell formation and gradient of involvement strongest at the adventitia and weakest at the intima (similar to GCA), and has been detected by some but not all investigators using molecular techniques in temporal artery biopsies [57, 58]. In epidemiologic studies, a retrospective review of administrative data in over 16 million adults, age over 50 years, and no previous GCA was able to identify almost 6000 cases of GCA [59]. An antecedent herpes zoster infection was documented in 3.1–6.0% of cases in the two datasets used. In a multivariate analysis, the increased risk of complicated herpes zoster followed by GCA had a hazard ratio of 1.99 (95% CI 1.32–3.02) and 2.16 (95% CI 1.46–3.18) in the two datasets. This roughly twofold increase in risk of GCA after a specific viral infection is clearly only one of the possible triggers of GCA.

Human papilloma virus DNA has been identified in 16 of 22 temporal artery biopsy samples, but other studies seeking *Chlamydia pneumoniae*, parvovirus B19, and herpesviruses in biopsy samples showed no difference between GCA patients and controls [60]. In addition, a recent microbiome study on GCA biopsy samples showed no increases in individual microorganisms [61].

Vasculitis: Polyarteritis Nodosa

Polyarteritis nodosa (PAN) related to viral infection has been recognized as having a separate pathogenesis from classic PAN. The best-studied is hepatitis B infection, but hepatitis C virus, HIV, human T cell leukemia virus-1, cytomegalovirus, EBV, and parvovirus B19 are additional associated agents [62]. The association of HBV with PAN is relatively common, with 10–54% of PAN cases in various series proven to have HBV, although the incidence has been decreasing in areas of higher HBV immunization [56, 63]. The vasculitis often occurs in the first 6 months of infection when both viral replication and the host's antibody formation are most active. This results in two proposed pathogenic mechanisms for the vasculitis: (1) toxicity to the vessel wall by direct invasion of virus and (2) IgG-containing immune complex and complement deposition at the endothelium with damage resulting from the immune response [62]. Nevertheless, demonstration of hepatitis B viral antigen in vessel walls has rarely been successful, making immune complex deposition the more common mechanism of vasculitis [64]. By contrast, classic PAN is associated with activation of both innate and adaptive immune pathways but without the prominent immune complex deposition [65].

Vasculitis: Cryoglobulinemic Vasculitis

Rheumatologists are often consulted on mixed cryoglobulinemia related to hepatitis C infection. Now in the era of direct-acting antiviral therapy for hepatitis C, the cryoglobulinemia and cryoglobulinemic vasculitis greatly improve or resolve after achieving a sustained virologic response. However, persistent cryoglobulinemia has been described in up to 20% of patients up to 2 years after viral cure [66]. In addition, patients with cryoglobulinemic vasculitis and cirrhosis may have delayed clearance of virus and remain at risk of vasculitis relapse despite HCV eradication. In all such cases cryoglobulins were present before antiviral treatment, so that HCV-related cryoglobulinemia is not known to begin de novo after successful HCV clearance [67].

Besides HCV, cryoglobulinemic vasculitis is occasionally identified in association with other viral infections. A French nationwide survey and additional literature review identified 45 patients with non-HCV cryoglobulinemic vasculitis with eight patients having a viral association, including four with HBV and one each having CMV, EBV, parvovirus B19, and HIV [68].

Evaluating for Viral Infection Versus Rheumatoid Arthritis

Most transient arthralgias related to an acute viral infection resolve without specific treatment in 6 weeks. Even when joint symptoms persist past this 6-week mark, a viral infection is not a common diagnosis made by rheumatologists. In a study of 322 patients presenting with less than 1 year of polyarthralgias or inflammatory arthritis, only 2 (0.6%) were diagnosed with a viral etiology (one HCV and one parvovirus B19) [69]. In a Finnish study of 60 patients with acute reactive arthritis, parvovirus B19 was found in only 3% of subjects [70].

Rheumatoid arthritis (RA) is in the differential diagnosis for viral infections that give persistent symptoms for more than 6 weeks regardless of viral clearance. The clinician commonly considers hepatitis C or HIV and uncommonly includes CHIKV, Ebola virus, and HTLV-1 (Table 9.1) [71]. The travel history as well as sexual and drug use history will be informative for gauging the initial likelihood of these viral infections. The clinical presentation of viral arthritis can be very similar to RA, with a small joint polyarthritis, elevation

of inflammatory markers (but viral infection sometimes leaves acute phase proteins and complement remarkably unchanged), and even positivity for RF and aCCP in 5–10% of CHIKV cases [8]. However, the marginal erosions of RA are generally not part of the presentation in viral arthritis.

The inflammatory syndrome seen in viral arthritis and rheumatoid arthritis can have similar pathophysiologic mechanisms. For example, alphaviruses such as Ross River virus and CHIKV can cause macrophage recruitment to joints, prominent intraarticular secretion of inflammatory cytokines and chemokines, with further recruitment of inflammatory infiltrates, all resulting in an amplification loop of inflammation [72]. The pathogenesis includes upregulation of the transcription factor NF-κB and production of the cytokines TNFα, IFN-γ, and MCP-1, all contributing to a proinflammatory environment.

Determination of anticitrullinated peptide antibody (ACPA) status has become a valuable diagnostic tool in assessing for rheumatoid arthritis in the setting of viral infection [73]. For the diagnosis of rheumatoid arthritis, anti-CCP antibodies have a specificity of 94% and a sensitivity of 70% [74]. Nevertheless, ACPAs from RA patients can also demonstrate cross-reactivity as shown in a BLAST search using the essential epitopes recognized by ACPAs. The amino acid sequences recognized by ACPAs were also found in 56 viral, 1,383 fungal, and 547 bacterial proteins and were recognized in vitro by ACPAs in the cases tested [75]. Anti-CCP antibodies are found in up to 33% of patients with HCV-related arthralgia/arthritis, a subgroup representing about 4% of all hepatitis C patients [76]. Patients with HCV infection but no joint symptoms rarely show aCCP positivity. By comparison, RF can be found in 50–80% of patients' HCV-related arthralgia/arthritis and in 9.7% of HCV patients without joint symptoms [77]. Titers are usually low to intermediate in viral infections compared to the highest levels seen in inflammatory arthritis. Therefore, there will be a small group of true rheumatoid arthritis patients among the HCV+ population, and these can be recognized more easily if they show the somewhat RA-specific features of high anti-CCP titers, erosive disease, and rheumatoid nodules [78]. The detection of multiple autoantibodies in HCV+ patients additionally includes ANA, SSA and SSB, anti-DNA, p-ANCA and c-ANCA, and anticardiolipin, demonstrating the wide immunoreactivity induced by viral infection [78].

Persistence of alphavirus particles or viral antigens in joint tissues is linked to chronic joint symptoms due to the six so-called "arthritogenic alphaviruses": Chikungunya virus (CHIKV), Barmah Forest virus (BFV), Mayaro virus (MAYV), Ross River virus (RRV), o'nyong-nyong virus (ONNV), and Sindbis virus (SINV) [5]. Alphaviruses are known to persist in tissue sanctuaries where they may evade immune clearance long term. For CHIKV, one report in humans demonstrated viral antigens in macrophages and viral RNA in synovial tissue 18 months after initial viral infection [79]. These findings have not been confirmed by subsequent studies, but ongoing IgM serologic responses have been shown to persist up to 6 months [80]. The result may be ongoing virus production, long-term IgM antiviral responses in the host, and more chronic clinical illnesses that may include a true arthritis. Reactivation of virus also becomes a concern whether due to immune suppression (chemotherapy, organ transplant, arthritis treatment) or other senescence and weakening of the immune system [81].

EBV is a further chronic viral infection that may show mechanisms related to RA development. EBV resides lifelong as a latent infection in the resting B cells of most individuals. Citrullinated proteins derived from EBV nuclear antigen (EBNA) can give rise to ACPA responses years before the onset of clinical rheumatoid arthritis. In addition, they cross-react with citrullinated fibrin and, therefore, show further features of ACPA responses relevant to RA pathogenesis [82].

Increased Viral Infection in Patients on Tofacitinib

While the risk of bacterial, fungal, and mycobacterial infections has received extensive attention with use of biologics in rheumatic diseases, the risk of viral infections is much less well studied. Recently, the mechanisms by which tofacitinib reduces antiviral responses have been examined in detail, focusing on in vitro plasmacytoid dendritic cells (PDC) and their production of interferon alfa (IFN-α) [83]. In an in vitro culture model using human cells, the authors found that tofacitinib induces PDC apoptosis by inhibiting expression of the antiapoptotic molecules, BCL-A1 and BCL-XL. In addition, tofacitinib strongly inhibited the production of IFN-α by toll like receptor (TLR)-stimulated PDCs. Also, tofacitinib suppressed the IFN-α-induced upregulation of TLR3 on synovial fibroblasts, thus inhibiting their cytokine and protease production in response to TLR3 ligation. Tofacitinib also counteracted the reduction of viral replication that otherwise results from the presence of IFN-α. Overall, tofacitinib leads to decreased production of IFN-α, decreased downstream cytokine and protease production from IFN-α, and permits increased viral replication. These mechanisms may help to explain the increased viral infection rates seen in patients on tofacitinib.

Vaccination and Autoimmunity

The same mechanisms that were discussed above for viruses to cause autoimmunity are relevant to viral vaccines and autoimmunity: genetic susceptibility, environmental factors,

a break in tolerance, molecular mimicry of the vaccine's viral protein compared to host antigens, and downstream activating mechanisms such as cytokine effects, bystander activation, polyclonal activation, and epitope spreading. The adjuvant used in a vaccine is an important participant in the impairment of immune tolerance. Most vaccines would not elicit an immune response without an adjuvant, indicating that the human immune system is inherently tolerant of many different pathogenic proteins and nucleic acids. Once immune tolerance to the pathogens is broken by the adjuvant, a neutralizing immune response becomes feasible.

Antiphospholipid Antibodies: Viruses and Vaccinations

Formation of antiphospholipid antibodies has been described after infection with hepatitis B virus, hepatitis C virus, HIV, varicella-zoster virus, rubella, CMV, and parvovirus B19 [84]. There has subsequently been interest in evaluating the induction of APL antibodies by vaccines.

The presence of chronic HBV infection triggers the formation of antiphospholipid antibodies. In one study of 50 HBV patients, anticardiolipin IgG was seen in 12.6%, β2GPI in 2.1%, and lupus anticoagulant in 1.4% of subjects. A meta-analysis has confirmed the elevated risk of aCL and β2GPI development in HBV patients [85, 86]. A recent study reported the risks of APL antibody formation in healthy controls versus virus-infected individuals. The findings showed increased relative risks of elevated anticardiolipin levels in virally infected patients: HIV with RR 10.5 (95% CI 5.6–19.4), HCV with RR 6.3 (95% CI 3.9–10.1), hepatitis B virus RR 4.2, (95% CI 1.8–9.5), and Epstein-Barr virus RR 10.9 (95% CI 5.4–22.2) [87]. These risks were clinically important as thromboembolic events were increased in patients with elevated aPL antibodies who had HCV (9.1%, 95% CI 3.0–18.1) and those with HBV (5.9%, 95% CI 2.0–11.9). HIV has separately been shown to lead to arterial and venous thrombotic events and HIV vasculopathy [88].

In studies of susceptibility to antiphospholipid syndrome after hepatitis B vaccination, a group of 85 healthy students was immunized [89]. One month later, 8 of 85 (9.4%) showed an increased titer of IgG anti-β2GP1. A potential mechanism was the binding of recombinant hepatitis B sAg to the fifth domain of the β2GP1 antibody, leading to induction of antibody production. No thromboembolic event occurred in this short-term study. A clinical trial of HBV immunization of lupus patients also showed no increase in lupus flares following immunization [90].

Influenza immunization was shown to elicit new formation of anticardiolipin but not β2GP1 antibodies but at the same rates in SLE patients (12 of 101 cases) as in healthy control (7 of 101), p = not significant [91]. Three meta-analyses showed no consistent adverse impacts of influenza immunization on SLE patients [92].

Starting almost 60 years ago, polio, smallpox, and mumps vaccinations were reported to elicit a transient rise in RF production in healthy individuals, but without clinical sequelae [93]. More recently, influenza vaccine has been shown to elicit a large number of autoantibodies (RF, ANA, ENA, ANCA, APL and others) in healthy subjects as well as autoimmunity patients but a transient increase in titers and lack of long-term autoimmunity are the rule [94]. Exceptions are coming to attention at the case report level and will require future follow-up [95].

Mechanisms of Vaccine Adjuvant Action

A reaction against a vaccination can come from the viral sequences used or from the adjuvant [96]. Adjuvants are essential since immunization with viral protein or nucleic acid alone would not elicit a protective immune response. The main adjuvants used in human vaccines are alum (aluminum salts), oil in water emulsions (MF59, AS03), and AS04 (theTLR4 ligand monophosphoryl lipid A absorbed to alum) [97]. Adjuvant activity has also been postulated to reside in bacteria, oils, drugs, silicone, and other environmental agents [98]. Multiple mechanisms of action have been investigated for adjuvants, starting with activation of innate immune mechanisms and downstream coupling to adaptive immunity. Aluminum stimulates dendritic cells to enhance antigen presentation, stimulates TLRs, promotes eosinophil activation, serves to attract neutrophils, and enhances production of chemokines and cytokines [99]. Evidence has been presented that alum might signal through the pattern recognition receptors (PRR) of the innate immune system and downstream activate the NLRP3 inflammasome and caspase1 [100]. The inflammation-induced local accumulation of uric acid may represent a damage-associated molecular pattern (DAMP) and act as an endogenous adjuvant capable of recruiting dendritic cells and activating T cells at sites of immunization [101]. The cytotoxicity induced by alum additionally releases host DNA, which is a further DAMP [102]. In an effort to improve the specificity of adjuvant targeting, newer adjuvants are under development as agonists for specific toll-like receptors, including TLR3, TLR4, TLR5, TLR7/8, and TLR9 [97].

Arthritis and Vaccinations

When live viruses are used as strains for vaccination, their growth and survival properties may result in articular manifestations in some instances. Rubella virus vaccine and an Ebola vaccine candidate serve as examples.

Rubella Virus and Rubella Vaccine

Rubella virus causes joint symptoms in up to 60% of those infected with worse symptoms in women [103]. Joint symptoms typically resolve within a few weeks yet an occasional patient will have episodic or chronic arthropathy that lasts months to years [104]. Multiple mechanisms have been invoked to explain long-term joint findings after rubella infection. Age, female gender, and MHC type all contribute to susceptibility. Rubella virus has been isolated in synovial fluid for up to a month following initial infection. The virus can be isolated from PBMCs of symptomatic individuals up to 6 years after infection and thus could be trafficked into joints. In vitro, rubella virus can be grown in primary human synovial tissues and in chondrocyte-derived cell lines, providing a mechanism for viral replication within the joint itself. The initial rubella virus infection may not be cleared despite a high-level antibody response by the humoral immune system. This raises the possibility of immune complex formation and deposition within the joints. Thus, there are both intra- and extraarticular reservoirs of rubella virus that can contribute to chronic symptoms.

The rubella vaccine is a live, attenuated virus that has a reduced capacity to replicate in synovial tissues and chondrocytes compared to wild-type virus. Rubella vaccination causes a similar range but decreased severity of joint symptoms compared to natural rubella infection, with arthralgias in 25% of recipients and frank arthritis in 1% [105]. At the extreme, rubella vaccination has been reported to be associated with a chronic arthritis lasting at least 1 year [106]. The virus has been detected in vaccinated women with a chronic arthropathy by using RT-PCR on PBMCs [107]. Although the incidence of chronic arthritis in rubella-vaccinated individuals is very low, specific HLA-DRB1 (DR2 and DR5) haplotypes may represent a genetic risk factor for chronic joint symptoms [108]. Despite some similarities in presentation, rubella vaccination is not a known cause of rheumatoid arthritis [107, 109].

Ebola Vaccine

The search for an Ebola virus vaccine has allowed controlled experiments that provide insight into requirements for arthritic manifestations after viral infection [110]. A candidate Ebola vaccine (rVSV-ZEBOV) was produced by adding Ebola surface glycoprotein (ZEBOV) to a vesicular stomatitis virus (VSV). Three observations shed light on Ebola's arthritogenic effects. First, the vaccination virus rVSV-ZEBOV showed a tropism for synovial tissue, even though wild-type VSV alone does not. Second, expression of the viral ZEBOV protein was not sufficient. Instead, viral replication may be needed to cause arthritis. A replication-deficient vector encoding ZEBOV (Chimp adenovirus type 3-ZEBOV) did not cause arthritis despite expression of ZEBOV. Third, the development of arthritis after virus exposure requires a competent host immune system. For multiple viruses, development of arthralgias and arthritis may actually occur at a time of convalescence, once the adaptive immune response is already robust and has partly or fully cleared the virus. A similar situation applies to vaccine viruses, which may cause arthralgias and arthritis at 2 weeks post vaccination, even at a time when any live vaccine virus is cleared and the host response to the vaccine's viral determinants is well established. Of course, exceptions such as rubella do exist with prolonged persistence of viral particles being associated with a more chronic arthritis.

Hepatitis B Vaccine

Recently, a hypothesis was put forward that nonresponders to hepatitis B vaccine might be at risk for developing autoimmune disease [111]. The theory rests on the observation that HBV nonresponders have higher Th1 cytokine responses such as IL-18 and IFN-γ. These same cytokines are also implicated in the onset of multiple autoimmune conditions including rheumatoid arthritis, systemic lupus, type 1 diabetes, and celiac disease. Further evidence is needed to substantiate this hypothesis.

Vaccines and Autoimmunity: ASIA Syndrome

A focus on adjuvants has resulted in the definition of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome in 2011 [112]. The hypothesis is that adjuvants activate the innate immune system and cause multiple downstream inflammatory and even autoimmune effects. An adjuvant might mimic evolutionarily conserved molecules such as bacterial cell wall, lipopolysaccharide, or unmethylated CpG DNA, allowing binding to Toll-like receptors. In turn, this could cause activation of dendritic cells and macrophages, initiating chemokine and cytokine release locally and from downstream T cells and mast cells. In those with defective regulatory circuits or other genetic susceptibility, immune tolerance could be broken by this nonspecific activation of the immune system, leading to expansion of autoreactive lymphocytes and potentially the onset or unmasking of an autoimmune disease. Subsequently, the syndrome has been broadened to include a variety of exposures, including chronic exposure to silicone, tetramethylpentadecane, pristane, as well as multiple adjuvants [113].

Clinically, ASIA syndrome is described as typical or atypical features of autoimmune diseases occurring in genetically susceptible individuals after vaccination [114–116]. It is char-

acterized as having myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment, and memory loss. Four groups of individuals who might be susceptible to development of vaccination-induced ASIA syndrome have been proposed [117]:

1. Individuals with prior postvaccination autoimmune phenomena
2. Individuals with a medical history of autoimmunity
3. Individuals with a history of allergic reactions
4. Individuals with risk factors for autoimmunity (positive family history of autoimmune diseases, asymptomatic carriers of autoantibodies, certain genetic profiles).

Criteria requiring validation have been proposed for the ASIA syndrome [112]. The four major criteria were (1) an exposure to infection, adjuvant, or other stimuli before clinical manifestations, (2) clinical findings in muscle, joints (arthralgia, arthritis), chronic fatigue, neurologic findings, cognitive impairment, pyrexia, and dry mouth, (3) improvement once the inciting agent is removed, and (4) typical biopsy of involved organs. The four minor criteria are (1) antibodies directed at the adjuvant, (2) other clinical manifestations such as IBS, (3) specific HLA associations as in rheumatoid arthritis, and (4) development of an autoimmune disease.

Examples of ASIA Syndrome: HBV and HPV Vaccination

The association of autoimmune findings with previous immunizations remains a controversial topic. However, there are at least four examples of reliably vaccine-associated autoimmune reactions: Guillain–Barré syndrome after the 1976 swine influenza vaccine, immune thrombocytopenic purpura after measles/mumps/rubella vaccine, myopericarditis after smallpox vaccination, and narcolepsy with cataplexy after previous pandemic H1N1 influenza virus vaccination [93, 118].

Hepatitis B vaccine consists of recombinant hepatitis B surface antigen with aluminum hydroxide as the adjuvant. The immune or autoimmune reactions after hepatitis B vaccination have been presented by multiple groups. In studies of susceptibility to antiphospholipid syndrome after hepatitis B vaccination, a group of 85 healthy students was immunized [89]. 1 month later, 8 of 85 (9.4%) showed an increased titer of IgG anti-β2GP1. A potential mechanism was the binding of recombinant hepatitis B sAg to the fifth domain of the β2GP1 antibody, leading to induction of antibody production. A cohort of 93 patients who had the new onset of possible immune features after hepatitis B vaccination was examined by Zafir et al. [119]. The cohort was 70% female and all were seeking legal advice for their conditions. Twenty one percent had a personal or family history of autoimmunity. Onset of symptoms occurred a mean of 43.2 days after the last vaccination injection. A large spectrum of clinical involvement was found, including neurologic symptoms, systemic symptoms (fatigue, fever, weakness), musculoskeletal symptoms, and gastrointestinal symptoms. A new disease was diagnosed in a substantial proportion of the series: neurologic disease in 25.8% (e.g., multiple sclerosis, CIDP, Guillain–Barré), central pain syndrome (20.5%), SLE in 9.6%, and RA in 8.6%. The criteria proposed by the authors for ASIA syndrome were met in 80 of 93 (86%) patients.

Human papilloma virus vaccine also utilizes aluminum as an adjuvant. The occurrence of new and exacerbation of existing autoimmune phenomena have been reported after vaccination [120]. In an epidemiologic study based on the vaccine adverse event reporting systems, 2,207 possible cases of ASIA syndrome were identified for a rate of 3.6 cases per 100,000 doses of vaccine [121]. Common manifestations were fever (58%), myalgia (27%), and arthralgia/arthritis (19%). Reported severe findings were generally nonrheumatologic, such as postural orthostatic tachycardia, primary ovarian failure, immune thrombocytopenic purpura, acute cerebral ataxia, thyroiditis, and autoimmune hepatitis [122].

At the same time, the existence of ASIA syndrome has been disputed by some [90]. Ameratunga et al. pointed out that the category of environmental triggers and autoimmune phenomena leading to ASIA syndrome has expanded over time to now include macrophagic myofasciitis syndrome, the Gulf War syndrome, the sick building syndrome, silicone exposure, and the chronic fatigue syndrome. The authors focus on the aluminum-containing adjuvants in hepatitis B and human papilloma virus vaccines, which have been proposed as etiologic factors in some cases of ASIA syndrome. The authors further discuss that immunotherapy can use up to 500 times the amount of aluminum during a 3- to 5-year course of treatment but with no known association with ASIA syndrome. In addition, immunotherapy patients actually had a lower, not higher, rate of autoimmunity in a large pharmacoepidemiologic study. It is clear that large groups of vaccine recipients receiving a variety of vaccines and adjuvants will need to be studied to provide more clarity. Furthermore, current research is focusing on more targeted activation of the innate immune system by newer adjuvants with a goal of preventing nonspecific and autoimmune responses.

The National Vaccine Injury Compensation Program

Side effects from vaccine administration have long been recognized and ongoing litigation has led to the formation of the

National Vaccine Injury Compensation Program [123]. This mechanism has specified for potential compensation after certain vaccine side effects, with each having a time frame of occurrence after vaccination published in an "injury table." Multiple viral vaccines are on this list and potential side effects are specified for measles/mumps/rubella vaccine, rubella only vaccine, polio vaccines, and hepatitis B antigen–containing vaccine. Multiple other viral vaccines are listed without specifying individual side effects: varicella, rotavirus, hepatitis A, influenza, and human papilloma virus. Of these, the only specific mention of rheumatologic effects is a chronic arthritis that can occur 7 to 42 days after administration of rubella vaccine.

Three means have been established to qualify for compensation under the National Vaccine Injury Compensation Program [123]. (1) One must show that a specified injury found on the injury table occurred in the prescribed time interval. For example, this would be chronic arthritis starting 7–42 days after rubella vaccination. Meeting these criteria allows a legal "presumption of causation." However, multiple vaccines such as influenza and human papilloma virus have no specified injury and time course listed. (2) One must prove that the vaccine caused the condition, or (3) one must prove that the vaccine aggravated a preexisting condition. Therefore, if the injury from the vaccine is not on the injury table or no table injuries are listed for a particular vaccine, the petitioner must prove causation, which can be a difficult task. Also, in addition to meeting one of the three compensation qualifications, one must demonstrate that the injury lasted at least 6 months after the vaccination, resulted in a hospital stay or surgery, or resulted in death. No compensation is awarded if the court determines that there is greater evidence of a nonvaccine cause.

Conclusions

Viral infections frequently result in transient arthralgias but occasionally result in a long-lasting, even chronic, arthritis. With viruses such as rubella, mumps, and measles largely controlled through widespread immunizations, arthritic symptoms are increasingly recognized with emerging viruses such as CHIKV. Multiple factors control the growth of viruses and the host's response: viral properties, host characteristics including age and comorbidities, genetics, innate immunity, and adaptive immunity. Some viruses have characteristic target tissues that can include the joints, the salivary glands, and cells of the immune system. Autoimmune phenomena due to the presence of viral protein or nucleic acids are possible through immune responses such as molecular mimicry or by the production of autoantibodies. The adjuvants used in vaccines greatly augment host immune responses and at times lead to autoimmunity. The ASIA syndrome has been proposed as a set of clinical criteria to better classify the long-term symptoms reported by vaccine recipients.

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