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CHAPTER SIX

T Lymphocytes as Measurable Targets of Protection and Vaccination Against Viral Disorders

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International Review of Cell and Molecular Biology, Volume 342
ISSN 1937-6448
https://doi.org/10.1016/bs.ircmb.2018.07.006

Abstract

Continuous epidemiological surveillance of existing and emerging viruses and their associated disorders is gaining importance in light of their abilities to cause unpredictable outbreaks as a result of increased travel and vaccination choices by steadily growing and aging populations. Close surveillance of outbreaks and herd immunity are also at the forefront, even in industrialized countries, where previously eradicated viruses are now at risk of re-emergence due to instances of strain recombination, contractions in viral vector geographies, and from their potential use as agents of bioterrorism. There is a great need for the rational design of current and future vaccines targeting viruses, with a strong focus on vaccine targeting of adaptive immune effector memory T cells as the gold standard of immunity conferring long-lived protection against a wide variety of pathogens and malignancies. Here, we review viruses that have historically caused large outbreaks and severe lethal disorders, including respiratory, gastric, skin, hepatic, neurologic, and hemorrhagic fevers. To observe trends in vaccinology against these viral disorders, we describe viral genetic, replication, transmission, and tropism, host-immune evasion strategies, and the epidemiology and health risks of their associated syndromes. We focus on immunity generated against both natural infection and vaccination, where a steady shift in conferred vaccination immunogenicity is observed from quantifying activated and proliferating, long-lived effector memory T cell subsets, as the prominent biomarkers of long-term immunity against viruses and their associated disorders causing high morbidity and mortality rates.

1. INTRODUCTION

The world was forever changed by the introduction of vaccine against smallpox in the late 1700s, at the time protecting its first 100,000 individuals. This was the first demonstration that a vaccine could successfully eradicate viruses causing disorders and diseases that even when not lethal, still had

the potential to cripple both surviving populations and their surrounding geographical economies. Since that time, the occurrence of epidemics and outbreaks are now at lower risk, following the introduction of massive vaccination programs able to induce immune system targeting of viruses causing severe disorders affecting distinct geographical locations, and with many epidemiological reports demonstrating long-term efficacy of viral control of non-naïve populations.

Outbreaks of existing and emerging viral diseases or disorders vary widely in duration and frequency across geographical populations. Some can be predicted annually, while others may see decades between outbreaks, therefore driving the continuous epidemiological surveillance of associated infectious disorders, the development and implementation of targeting vaccines, and development of immune-monitoring strategies measuring vaccine efficiency in target populations. Despite vaccination-mediated protection of numerous nations documenting complete eradication of the causative agents of viral disorders in endemic populations, there is threat of re-emergence of pandemic proportions of these agents. Threats to virus re-emergence are caused by contemporary choices made to not vaccinate children, by strain recombination, by viral spread to naïve populations by world-travelers, migrants, or climate change, causing redistribution of viral vectors, by potential use of these agents in acts of bioterrorism or war upheaval, or by depletion of vaccination stocks required for protection against pandemics. Other factors include the increasing and aging global population and increased number of immunocompromised individuals—factors strongly supporting the maintenance of herd immunity against existing viruses, despite lower incidence of outbreaks in industrialized countries. In the event of a re-emergence of previously eradicated viruses or the acquisition of increased pathogenicity by existing viral strains, there is an urgent need for vaccine development strategies that can rapidly and effectively arrest global spread.

Important advances are continuously being made in vaccine development strategies toward the control of viruses and associated disorders. Vaccine design has been modified from the use of attenuated viruses to use of more precise viral protein subunits specifically targeted by T cells. Historically, vaccination immunogenicity was documented by measures of serum immunoglobulin (Ig) classes and antigen-specific antibodies produced by humoral immunity. More recently, quantification of cellular components of innate immunity at the interface between innate and adaptive immunity are made, in addition to more precise measurements of adaptive immunity.

Long-term protection achieved by adaptive immunity can be quantified by measuring levels of circulating cytokines, along with specific phenotypic profiles of effector memory, antigen-specific T cells. Though both humoral and cellular arms of immunity are integrally linked during the initial induction of immunity against pathogens, these can become disconnected with developing pathology due to their individual needs for survival factors, unequal declines in immune function, and differential cellular lifespans. This loss of correlation between memory T cells and neutralizing antibody responses varies according to different viruses, suggesting that independent time course measures of these separate immune responses are required over time for adequate recording of biomarkers of natural infection and vaccine efficacy or suggesting that T cell status may be most crucial measure of conferred long-term immunity.

From the standpoint of fundamental or clinical research, it has become established that the targeted induction of specific pathogen- and tumor-clearing effector memory T cell subsets is our endgame armor toward long-term human survival against infectious diseases and cancers. This chapter provides an overview of viruses that have historically caused severe lethal disorders, including those of the respiratory, gastric, skin, hepatic, neurologic, and hemorrhagic types. The features of viruses and associated disorders that we herein describe include viral genetics and replication cycles, transmission modalities, cell and organ tropism, host-immune evasion strategies, associated viral disorders and diseases, and epidemiology. We also report on well-accepted and other important documented instances of viral control by T cells, currently available and successful vaccines, and recorded measures of vaccination immunogenicity. We focus on quantification of vaccine-induced effector memory T cell—mediated immunity, representing the gold standard of successful vaccination. Just as it is for advances in vaccinology, investigations into the biology of T cells are currently at the forefront of many research fields examining various disorders, diseases, and malignancies not formerly considered to be controlled by immunity.

2. RESPIRATORY VIRUS DISORDERS

Although many viral infections are limited to the upper respiratory tract, it is lower respiratory tract infections (LRTI) that most predominantly cause enormous disease burden in children and immunocompromised adults suffering from human immunodeficiency virus (HIV) infection or in patients having received stem cell or solid organ transplants for which

immunosuppressive therapies were administered (Henrickson et al., 2004; Pavia, 2011; Kim et al., 2007). Acute lower respiratory illnesses (ALRIs) are a major cause of morbidity and mortality, accounting for approximately 1.6 million deaths, globally, per year (Black et al., 2010). Frequently overlapping LRTI syndromes include bronchiolitis, asthma exacerbation, wheezing, croup, and pneumonia. Although certain specific syndromes can be more precisely associated with infection by specific viruses, syndromes overlaps can complicate diagnosis of these numerous viruses, and quite often, difficulties in differentiating between viral and bacterial pneumonias symptoms can also result in antibiotics being mistakenly prescribed during viral disorders.

Several viruses are normally, however, considered to be primarily responsible for LRTIs, beginning with upper respiratory tract infections, most commonly caused by respiratory viruses that are typically spread from person-to-person by contact with infected respiratory droplets, and including respiratory syncytial virus (RSV), epidemic influenza A and B, H5N1 and H7N9 avian influenza A viruses (IAVs), parainfluenza viruses 1 through 4, adenovirus, human metapneumovirus (hMPV), severe acute respiratory syndrome coronavirus, human coronaviruses NL63 and HKU1, rhinoviruses, and bocaviruses (Pavia, 2011; Mahony, 2008; Nichols et al., 2008) (Table 1). Currently, vaccines for human influenza viruses, human parainfluenza viruses (HPIVs), and adenoviruses causing upper and lower respiratory infections are used to control these infections and the resulting propagation of their morbid symptom derivations.

2.1 Influenza Virus Classification, Epidemiology, Immunology, and Vaccinology

Human influenza viruses make up three of the five genera of the family *Orthomyxoviridae* and are classified as A, B, and C types, based on their highly conserved matrix protein 1 (M1), membrane matrix protein (M2), and nucleoprotein (NP). Type A influenza viruses can be further sub-subtyped by the antigenicity of their hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins (GPs). Antigenic drift, caused by point mutations in HA and NA and recombination of the HA genes, results in the generation of new strains that can escape pre-existing immunity, causing both the prediction of circulating strains difficult and antigenic mismatch by existing vaccines. Approximately 18 HA and 9 NA subtypes of influenza A are documented in aquatic birds, representing their natural hosts (i.e., vectors). Influenza A H1 and H3 subtypes cocirculate seasonally, and Influenza B

Table 1 Viral Disorders and Associated Viruses

	Principal Syndromes	Prevalence and Distribution	Specific Therapy	Specific Prevention
Respiratory infections	**Epidemic influenza viruses A, B, and C and avian influenza viruses**			
	Influenza AFRD Acute bronchitis and pneumonia Croup	A and B: Seasonal epidemics, occasionally pandemic C: Endemic Global	A and B: Oseltamivir or zanamivir	A and B: Vaccine, oseltamivir or zanamivir
		Avian H5N1 and avian H7N9: Poultry-associated	Oseltamivir	Avoiding contact with birds
	Parainfluenza viruses 1–4			
	AFRD Acute bronchitis and pneumonia Croup	1: Local epidemics 1, 2, and 3: Widespread in children	None	Vaccines under investigation
	Adenoviruses			
	AFRD Acute respiratory disease Acute pharyngoconjunctival fever Epidemic keratoconjunctivitis Viral pneumonia Acute follicular conjunctivitis Diarrhea Hemorrhagic cystitis	Global Mostly children	None	Vaccine in military populations
	Orthohantaviruses			
	Hantavirus pulmonary syndrome	North, Central, and South America	None	None
	Respiratory syncytial virus and human metapneumovirus			
	Lower respiratory illness Mild upper respiratory illness	Widespread in children	Ribavirin for immunocompromised patients	Palivizumab IM monthly (infants at high risk)
	Rhinoviruses			
	Common cold Acute coryza	Universal, especially during cold months	None	None
Exanthematous infections	**Rubeola virus**			
	Measles Encephalomyelitis CNS involvement	Global Incidence decreasing because of vaccine	None	Vaccines
	Rubella virus			
	German measles Birth defects during pregnancy	Universal	None	Vaccines
	Human parvovirus B19			
	Erythema infectiosum Rash, malaise, arthritis Hydrops fetalis Anemia	Sporadic outbreaks	IVIG (for severe anemia)	None
	Human herpesvirus type 6			
	Roseola infantum	Widespread Affects young children	None	None
	Varicella-zoster virus			
	Chickenpox	Before vaccine, universal in children, occasionally in adults	Acyclovir, famciclovir, valacyclovir	Immune globulins, vaccine
	Zoster	Common in adults, resulting from reactivation of latent virus	Acyclovir, famciclovir, valacyclovir	Vaccine
	Variola			
	Smallpox	Natural disease eradicated	Cidofovir Smallpox vaccine up to 4 days after exposure	Vaccine Cidofovir
	Alphaviruses			
	Chikungunya disease	Transmitted by *Aedes* mosquitoes Africa, Southeast Asia, India, Europe, the Americas	None	None
	Mayaro disease	Mosquito-borne South America, Trinidad, Haiti	None	None

	Ross River virus disease	Aedes mosquitoes Australia, Papua New Guinea, South Pacific	None	None
	Molluscum contagiosum virus			
	Molluscum contagiosum papules	Genital Exposed skin More severe in AIDS patients	Cryotherapy, curettage	None
Hepatic infections	**Hepatitis virus**			
	Hepatitis A	Widespread, often epidemic	None	Immune globulin, vaccine
	Hepatitis B	Widespread	Interferon, antivirals nucleoside/nucleotide analogs	Screening for hepatitis B surface antigen Vaccine, hepatitis B immune globulin
	Hepatitis C	Widespread	Interferon, ribavirin, direct-acting antivirals	Screening for hepatitis C
	Hepatitis D	Endemic pockets in several countries Parenteral drug users at relatively high risk Can infect only in the presence of hepatitis B	Interferon	None
	Hepatitis E	Outbreaks Genotypes 1 and 2: Developing countries Genotype 3: Europe Severe during pregnancy	None	Vaccine (not available in US)
Neurologic infections	**Polioviruses**			
	Poliomyelitis	Global	None	Vaccines: Live (oral), killed (injected)
	Aseptic meningitis	Incidence now low because of vaccine		
	Alphaviruses, mosquito-borne			
	Western equine encephalitis	North and South America	None	None
	Eastern equine encephalitis	North America	None	Vaccine available to protect equines Vaccine used in laboratory workers at risk
	Venezuelan equine encephalitis	Gulf states to South America	None	Vaccine available for equines Vaccine used in laboratory workers at risk
	Flaviviruses, mosquito-borne			
	Japanese encephalitis	Widespread	None	Vaccine
	Murray Valley encephalitis	Australia, New Guinea	None	None
	St. Louis encephalitis	North and South America	None	None
	West Nile virus encephalitis	Widespread	None	Screening blood and blood products
	Flaviviruses, tick-borne			
	Powassan encephalitis	Canada, eastern and upper midwestern US	None	None
	Tick-borne encephalitis	Europe, Balkans, former Soviet Union Outbreaks coincide with periods of tick activity	None	Vaccine available in Europe and Russia
	Orthobunyaviruses, mosquito-borne			
	California encephalitis	Probably worldwide Common in midwestern and eastern US Symptomatic infection primarily in children	None	None
	Mammarenaviruses			
	Lymphocytic choriomeningitis	US, Europe, possibly elsewhere Chief reservoir: House mouse Primarily in adults during autumn and winter	None	None
	Rabies virus			
	Rabies	Widespread	None	Vaccine Postexposure rabies immune globulin
	Flaviviruses			
	Omsk hemorrhagic fever	Former Soviet Union	None	None
	Kyasanur Forest disease	India	None	None
	Yellow fever	Africa, Central and South America	None	Vaccine for oubreaks and travellers
	Dengue fever	Tropics and subtropics, worldwide	None	Vaccine in phase 3 trials
	Orthohantaviruses			

(*Continued*)

Table 1 Viral Disorders and Associated Viruses—cont'd

Hemorrhagic fevers	Hemorrhagic fever	Northern Asia, Europe Seoul virus: In rat population worldwide	Ribavirin	None
	Filoviruses			
	Lake Victoria marburgvirus disease	Africa	None	None
	Sudan ebolavirus disease	Africa, Sumatra	None	None
	Bundibugyo ebolavirus disease	Uganda	None	None
	Zaire ebolavirus disease	Africa	None	Ring vaccination trials
	Reston ebolavirus disease	Philippines	None	None
	Mammarenaviruses			
	Lassa fever Bolivian hemorrhagic fever Argentinian hemorrhagic fever Venezuelan hemorrhagic fever Brazilian hemorrhagic fever	South America, Africa	Ribavirin Convalescent plasma for all except Lassa fever	Vaccine for Argentinian hemorrhagic fever
	Lujo virus disease	Zambia	None	None
	Orthonairovirus			
	Crimean-Congo hemorrhagic fever	Widespread	Ribavirin	Vaccine (efficacy unknown)

Assembled from Merck Manual, Professional Version: Types of viral Disorders

viruses can only infect humans, via two distinct, seasonally cocirculating, lineages. Type C influenza viruses are more rarely documented to infect humans and pigs (Berlanda Scorza et al., 2016).

Influenza viruses cause acute upper and lower respiratory infections, and due to their rapid and unpredictable genetic drift, represent the most likely of pathogens to cause a human pandemics. Annually, human influenza viruses have the potential to cause up to 5 million cases of severe illness, with an associated 500,000 deaths worldwide (WHO_Influenza_(Seasonal), 2018), causing great economic burden. Four influenza pandemics have occurred over the past century, as a consequence of the H1N1 (1918), H2N2 (1957), H3N2 (1968), and H1N1 (1977) variants (Palese, 2004). Since the most recent outbreak in 2009, an estimated 200,000 people globally have succumbed to the H1N1 variant of swine origin (Dawood et al., 2012).

Epithelial cells that are infected with influenza virus produce inflammatory cytokines acting as chemoattractants for homing macrophages and dendritic cells (DC). DCs take up influenza viral particles to trigger their maturation and pursuant migration to the lymph, where they initiate antigen-specific T cell maturation. These influenza-specific effector T cells then enter the respiratory tract to counteract viral titres through cytokine expression and the direct lysis of infected cells, with activated $CD8^+$ effector cytotoxic T cells (CTLs) representing the main constituents of this response by their release of perforins and granzymes, and the engagement of tumor necrosis factor (TNF) receptors (Spitaels et al., 2016). Influenza-specific $CD4^+$ T helper cells can act directly and indirectly in viral clearance, primarily by producing cytokines that induce the functions of B cells and $CD8^+$ T cells and which have also been reported to directly eliminate infected cells themselves (Topham and Doherty, 1998; Hua et al., 2013). While pre-existing $CD8^+$ T cell immunity has not yet been demonstrated to prevent infection from occurring, it is hypothesized to be the result of the loss of granzyme expression by memory $CD8^+$ T cells and populations of IAV-specific $CD8^+$ T cells are still importantly correlated with the control of spread and recovery in healthy populations (Grant et al., 2016). The most currently administered influenza vaccines are inactivated (IV) trivalent (TIV) or quadrivalent formulations containing equal amounts of HA of two influenza A strains (H1N1 and H3N2) and one of two influenza B strains (Yamagata and Victoria lineage). These are derived from viruses typically grown in fertilized chicken eggs, are mainly focused on eliciting a strain-matched humoral immune response—requiring yearly updates—and are unable to provide protection to all vaccinated individuals. The requirement

of memory T cell immunity for long-term protection against influenza virus promotes the development of vaccines that elicit both humoral and cellular immunity: a strategy expected to overcome the inadequacies of current vaccines against influenza and other viruses (Spitaels et al., 2016). There is broad interest in the development of a universal influenza vaccine, considered to be the "holy grail" of influenza vaccine research. This approach is being developed to use virus-infected cell-killing antibodies that produce an antiviral environment; these termed antibody-dependent cellular cytotoxicity (ADCC)-mediating antibodies, which are predicted to link innate and adaptive immune responses, and is becoming possible due to new technologies for rapid isolation and characterization of monoclonal antibodies targeting conserved regions of influenza virus, reviewed in Jegaskanda et al. (2017). This approach has been postulated to work, in part, from reports of IAV-specific $CD8^+$ T cells, promoting viral clearance in the absence of neutralizing antibodies, and can also mediate cross-reactive immunity against distinct IAVs to drive a rapid recovery from severe influenza disorders (Grant et al., 2016). The induction of infection-permissive immunity is both protective and allows virus-induced cross-reactive immune responses. Vaccines targeting the conserved ectodomain of M2 deliver this kind of non-neutralizing immunity since these antibodies rely on Fc receptors and innate immune components (El Bakkouri et al., 2011). Antagonizing antibodies inhibiting NA activity represents another promising strategy, not by blocking viral entry and eliciting sterilizing immunity, but by contributing to immunity against a virus possessing a similar NA type (Wan et al., 2013). There is also progress being made in the development of recombinant T cell—inducing vaccines, with the most advanced version of this strategy demonstrated by Modified Vaccinia Ankara (MVA) viruses expressing influenza virus NP and M1 antigens (Berthoud et al., 2011), with vaccinated individuals demonstrating increases in interferon-gamma (IFN-γ) expressing $CD8^+$ T cells and increased protection against influenza infection (Antrobus et al., 2012; Powell et al., 2013). Co-administration of this MVA-based vaccine with TIV formulations results in increased influenza strain—specific antibody responses and the generation of memory T cells that recognize a range of influenza A subtypes (Antrobus et al., 2014). Additional research demonstrates production of antigen-specific T cell responses using alternate prime/boost regiments of combinations of vaccination regimens employing recombinant replication-deficient adenovirus or MVA, expressing IAV NP and matrix protein 1 (Lambe et al., 2013). Quality and clonal T cell receptor (TCR) characteristics of influenza-specific $CD8^+$ T cells, in addition to in

silico predicted and peptide-based approaches for pools of minimal IAV epitopes, are investigated for their induction of cellular immunity and recognition by $CD8^+$ T cells (reviewed in Grant et al., 2016).

2.2 Parainfluenza Virus Classification, Epidemiology, Immunology, and Vaccinology

HPIV are enveloped negative-sense RNA genome viruses of 150–250 nm, belonging to the large and rapidly growing Paramyxoviridae family, causing significant human and veterinary disorders (Henrickson, 2003). HPIV is divided into serotypes 1 to 4, with HPIV-1 representing the most common etiologic agent of associated disease, but with HPIV-1, -2, and -3 representing common causative agents of respiratory illness in pediatric, geriatric, and immunocompromised populations (Schmidt et al., 2011).

HPIVs are a common cause of acute respiratory illness throughout all stages of human life (Schomacker et al., 2012), causing acute respiratory infections in children (Cooney et al., 1975). Second, only to human respiratory syncytial virus, HPIVs are the major contributors to hospitalization due to ALRIs and global pneumonia mortalities in young children, and up to 80% of children are seropositive for HPIVs by the age of 5 years (Murphy, 1988; Weinberg et al., 2009). HPIV infections can induce potent humoral and cellular immune responses, including innate immune responses, local and systemic IgG and IgA responses, and adaptive $CD8^+$ and $CD4^+$ T cell responses (Gitlin et al., 2010; Hou et al., 1992). Though cellular responses can restrict HPIV replication dynamics and clear primary infections, neutralizing antibodies against virus envelope hemagglutinin-neuraminidase (HN) and fusion (F) GPs are required for early infection (Suzuki et al., 2001; Zhang et al., 2005) and confer long-term protection against HPIV-related disorders (Murphy, 1988; Spriggs et al., 1987; Schmidt et al., 2011). Currently, there is no vaccine to protect against human HPIV infection. Progress in the development of HPIV vaccines using reverse genetics for serotypes −1 to −3 has generated several live-attenuated, intranasal HPIV vaccines evaluation in adults and in children, two of which, HPIV-3 are well tolerated in HPIV3-seronegative pediatric populations (Schmidt et al., 2011). Ongoing pediatric trials testing live-attenuated HPIV vaccines for HPIV-1 and HPIV-2 predict these will replicate in the upper respiratory tract of infants to induce the full spectrum of humoral and cellular immune responses (Karron et al., 2015). Heterologous (i.e., Jennerian) vaccine design strategies using the Sendai virus (SeV) to control infections by HPIVs and RSV are discussed in the following section.

2.3 Respiratory Syncytial Virus Classification, Epidemiology, Immunology, and Vaccinology

Human respiratory syncytial virus (RSV) types A and B are found within the genus *Orthopneumovirus*, family *Pneumoviridae*, of the order *Mononegavirales*. RSV is an enveloped, spherical virus of ~150 nm in diameter, and reaching up to several micrometers in length (Gower et al., 2005). The negative-sense RNA genome encodes for outer structural, NP, polymerase, NS, transmembrane, and regulatory proteins (Griffiths et al., 2017).

RSV is a major cause of ALRIs, resulting in numerous pediatric hospitalizations globally, where by 3 years of age, most children have been exposed and are at risk of developing life-threatening bronchiolitis and pneumonia (Glezen et al., 1986; Hall et al., 2009; Henrickson, 1994). Up to 120,000 infants are hospitalized due to RSV infection in the United States (Marks, 1992), and 34 million episodes of RSV-associated ALRI in children globally represent at least 3 million cases resulting in hospitalization, and approximately 199,000 associated deaths per year (Nair et al., 2010).

A balance of adaptive immune CTLs and neutralizing antibodies of the humoral immune response mediate protection and clearance of RSV infection (Griffiths et al., 2017). Though neutrophils are the highest proportion of leukocytes found in the airways of those infected with RSV (Everard et al., 1994), and despite observations that natural killer (NK) cells are first to attain infected airways (Hussell and Openshaw, 1998), it is $CD4^+$ helper and $CD8^+$ CTLs that correlate with the early clearance of RSV-infected cells (Anderson et al., 1990). In infants and immunocompromised populations, fatalities resulting from RSV infection are associated with deficiencies in $CD4^+$ and cytotoxic $CD8^+$ T cells (Hall et al., 1986; Welliver et al., 2008). Later in infection, increases in neutralizing antibodies prevent reinfection by opsonizing viral epitopes required for RSV entry and infection, and RSV clearance can be associated with RSV-neutralizing nasal Immunoglobulin A (IgA) (Mcintosh et al., 1978). More recently, enhanced RSV clearance with reduced disease severity has been associated with vaccine-elicited memory $CD8^+$ T cells (Lee et al., 2012). While memory $CD8^+$ T cells can mediate protection against RSV infection, in the absence of antibodies and memory $CD4^+$ T cells, these cause mortality via systemic proinflammatory cytokine storms and local IFN-γ production (Stoley et al., 2016; Schmidt et al., 2018). Other recent studies however indicate that the $CD8^+$ T cell response may not be the major determinant of severity of RSV-related pathology (Collins and Melero, 2011).

There are currently several recombinant RSV subunit vaccines in clinical trials, including the Novavax RSV F Vaccine representing the most promising candidate for licensing. This RSV F subunit targeting vaccine has been demonstrated to elicit the expression of circulating neutralizing antibodies against RSV (Glenn et al., 2016). Toward the development of future adaptive immunity-inducing RSV vaccines, it has been demonstrated that the transfer of airway-resident T cells protect against RSV, where it has been suggested that, to lessen the burden of T cell—mediated damage to airways, the induction of lung tissue T cells should be the focus of vaccine development (Kinnear et al., 2018).

Recently, the SeV has been used as a component of a Jennerian vaccine model for HPIV-1 and as a backbone for other viruses causing serious lower respiratory infections (LRIs), including other HPIVs, RSV, and hMPV. SeV-based vaccines have proven to be effective toward inducing B cell and T cell immune responses, and in the protection from HPIV-1, -2, and -3, and RSV, where they can also be used in combination with other vaccines to prime—boosts or to target one or more than one paramyxovirus pathogen (Russell and Hurwitz, 2016). SeV is attractive for use in human vaccination because it is a murine pathogen unable to infect humans (Bousse et al., 2006) and therefore does not require attenuation as it can never revert to a human pathogenic phenotype (Schickli et al., 2012). Another important feature supporting the use of SeV as a pan-virus vaccination agent stems from its ability to grow transiently in mammalian cells, accommodating the endogenous expression of antigens with posttranslational modifications matching those of the target antigens and neutralizing epitopes (Henrickson et al., 1991), with endogenous expression of antigens ensuring robust activation of $CD8^+$ T cells able to destroy antigen-producing cells and terminate virus amplification (York and Rock, 1996; Russell and Hurwitz, 2016). In murine studies, SeV could elicit rapid and durable respiratory mucosa and systemic HPIV-specific B cell and T cell responses (Sealy et al., 2010; Rudraraju et al., 2011). Clinical testing of human populations infected with RSV and HPIVs is underway (Adderson et al., 2015). For a full review of current development of antiviral compounds and vaccine candidates tested against RSV, see Costello et al., 2012.

2.4 Adenovirus Classification, Epidemiology, Immunology, and Vaccinology

Human adenoviruses (HAdVs) are classified in the *Mastadenovirus* genus, containing seven known HAdV species, from HAdV-A to HAdV-G, and

with at least 57 unique known human serotypes (Buckwalter et al., 2012). Adenoviruses are nonenveloped double-stranded DNA viruses ranging from 65 to 80 nm in diameter and are composed of a protein capsid, a NP core, and internal proteins. DNA homology between HAdV subgroups ranges from 48% to 99% (Walls et al., 2003).

HAdV infection rarely causes serious or fatal illness in immunocompetent individuals but may cause severe disease in immunocompromised, pediatric, and geriatric populations (Lynch et al., 2011). Clinical disease symptoms associated with HAdVs are dependent on HAdV genotypes, with at least 69 recognized, and assigned to subgroups A through G. Clinical symptoms include fever, rhinorrhea, pharyngitis, conjunctivitis, gastroenteritis, bronchitis, pneumonia, acute hemorrhagic cystitis, and meningoencephalitis (Lynch et al., 2011). Recombination between HAdVs are largely responsible for outbreaks of acute febrile respiratory disease in immunocompetent military recruits, where serotypes 4 and type 7 have been documented to account for approximately 60% of these respiratory illnesses (Hilleman et al., 1957; Dudding et al., 1973), and are associated to other frequently occurring disorders including upper and lower respiratory illnesses, gastroenteritis, hepatitis, keratoconjunctivitis, meningoencephalitis, cystitis, and myocarditis in these immunocompetent populations, reviewed in Lion (2014). Adenoviruses are endemic in pediatric populations (Echavarria, 2008). The incidence of adenovirus infection peaks in infants and children, where, globally, 5%–7% of respiratory tract infections in pediatric patients are ascribed to HadV (Ghebremedhin, 2014). Recently, re-emergence of type 7d HAdV has caused fatal outbreaks due to severe pneumonia syndromes in children from high-density populations (Yu et al., 2016).

Immune responses to adenovirus infection are dependent on primary sites of inoculation, methods of transmission, viral serotypes, and secretory Ig antibody status of the infected host; IgAs are present in respiratory tract early following infection, and IgG2 is present in serum and nasal secretions at later time points, reviewed in Walls et al. (2003). Histopathological changes resulting from infection can be divided into two phases: The first phase of immune histopathology predominantly involves nonspecific, cytokine-mediated inflammatory recruitment of monocytes and macrophages, while the second phase involves T cell infiltration (Prince et al., 1993). T cell–mediated immunity is believed to be required for HadV recovery from acute infections, and individuals lacking adaptive immunity are found to be at elevated risk of infection, with $CD8^+$ T cells as primary mediators of response to respiratory viruses, with relatively little contribution

by $CD4^+$ cells (Woodland et al., 2001). However, following adenovirus exposure, $CD4^+$ T cells have been shown to be responsible for increasing proliferation status of peripheral blood mononuclear cells (PBMC), and $CD4^+$ T cells represent the major CTL subsets produced and recognize conserved antigens across adenovirus serotypes (Flomenberg et al., 1995; Regn et al., 2001). Adenoviruses have, however, evolved several host-evasion strategies, including inhibition of apoptosis, responses to IFN-γ and TNF-α, and major histocompatibility complex (MHC) class I expression (Mahr and Gooding, 1999; Wold et al., 1994, 1999).

The live, oral adenovirus vaccine was licensed in the 1970s for active immunization toward the prevention of febrile acute respiratory disease in military populations, where it initially reduced adenovirus-associated respiratory illnesses by over five-fold (Dudding et al., 1973). Vaccine stock depletion and associated epidemics led to the manufacture of another vaccine in 2011, again denting adenovirus-associated disease burden by approximately 100-fold among recruits within the first 2 years of its introduction (Radin et al., 2014). These oral lyophilized vaccines replicate asymptomatically in the gut, inducing humoral and cell-mediated immunity, to confer long-lasting protection from infection (Berg et al., 2014). Due to their abilities to induce potent transgene product-specific T- and B-cell responses, adenovirus vectors are explored for use as vaccine carriers against a variety of many other pathogens (Chen et al., 2010; Harro et al., 2009; Hill et al., 2010; Radosevic et al., 2007).

2.5 Respiratory Virus Disorders and Adaptive Immune Responses Summary

ALRIs by respiratory viruses are a major cause of morbidity and mortality, accounting for over 1.5 million deaths globally each year, and are predominantly resulting from human transmission of virus containing respiratory droplets. Licensed vaccines are useful against several viruses causing these severe, often lethal, associated disorders. Influenza has no borders and causes great economic burden, making it a prominent international concern. Its rapid and unpredictable genetic drift causes human pandemics, where it has an annual potential of causing 5 million infections and 500,000 deaths worldwide. Influenza vaccinology requiring constant yearly updates has stimulated interest in the development of universal T cell vaccines that can elicit both humoral and cellular immunity, whereby influenza-specific memory $CD8^+$ T cell responses against a range of influenza subtypes could be induced to clear infection in absence of neutralizing antibodies.

RSV causes 34 million ALRIs in children annually, resulting in 3 million hospitalizations and almost 200,000 deaths per year. RSV is cleared by balance of adaptive immune CTLs and humoral neutralizing antibody responses, correlating most highly with $CD4^+$ helper and $CD8^+$ CTLs during natural infections, and with memory $CD8^+$ and $CD4^+$ T cells following vaccination, with research endeavours targeting their strengthening by specific induction of lung tissue RSV targeting T cells. Second, only to Rsv, Hpivs cause many ARI- and LRI-associated mortalities in children. HPIVs can induce potent humoral, innate, and adaptive $CD8^+$ and $CD4^+$ T cell responses able to restrict their replication and where neutralizing antibodies can confer long-term protection against their associated disorders.

HAdVs infect both immunocompetent and immunocompromised humans and have been shown to cause up to 60% of respiratory disorders in hospitalized military personnel. Despite their having evolved convoluted host-evasion strategies, adaptive T cell immunity against HAdVs starts early in diseases phases and is key to recovery from acute natural infection, with its greatest contributions by cytotoxic $CD8^+$ T cells that require stimulating by $CD4^+$ T cells for their expansion. Vaccines against HAdVs induce both humoral and adaptive immunity, including potent transgene virus-specific T- and B-cell responses conferring long-term protection. Success from HAdV vaccinology has influenced explorations of adenovirus vectors as target carriers for vaccination against numerous other pathogens.

3. VIRAL GASTROENTERITIS DISORDERS

Diarrheal disorders remain a leading cause of morbidity and mortality worldwide, with these listed in the top five causes of death worldwide, and which are associated with global estimates at 4—6 million deaths per year; reviewed in Clark and Mckendrick (2004). The majority of gastric infections are viral in origin, and viral gastroenteritis is one of the most common illnesses in all age groups and an important cause of morbidity in industrialized countries (Chang et al., 2003). The human risk of viral gastroenteritis in the United States alone is at least one per individual per year, with 450,000 adults and 160,000 children hospitalizations recorded and an associated 4000 mortalities per year (Mead et al., 1999; Mounts et al., 1999). Several viruses are responsible for viral gastroenteritis, where their transmission typically occurs from person-to-person by the oral-fecal route. Viruses commonly causing gastroenteritis include rotavirus (RV; causing the most serious gastric disorders), norovirus, astrovirus, adenovirus, and coronavirus-like agents (Table 1).

3.1 RV Classification, Epidemiology, Immunology, and Vaccinology

RVs are classified as a genus within the family *Reoviridae*. These are nonenveloped viruses measuring 70 nm in diameter and have inner and outer capsids surrounding their cores containing double-stranded RNA viral genomes encoding viral capsid (VP-1 to VP-6, and VP-7; VP4 outer capsid protein mediates virus attachment to cells) (Bishop et al., 1973) and nonstructural (NSP-1 to NSP-6) proteins, reviewed in Desselberger (2014). RVs classify into seven serotypes (A–G), based on antigenic properties of the inner capsid VP6 protein, where subtypes A–C represent human pathogens and are further subclassified into serotypes within these groups on the basis of differing outer capsid composition (Anderson and Weber, 2004; Wilhelmi et al., 2003).

Diarrhea is a major cause of death among children globally (Liu et al., 2012), and RV is the leading cause of severe diarrhea, globally causing an estimated 453,000 deaths in developing countries and 2.3 million pediatric patient hospitalizations (Tate et al., 2012; Parashar et al., 2003). RV also represents a significant cause of disease in industrialized countries, with greater numbers of hospital admissions reported relative to developing countries (Chang et al., 2003). Though Group A RV causes the majority of endemic infections and can also lead to significant outbreaks in infant and geriatric populations (Villena et al., 2003; Marshall et al., 2003), group B RVs are less common but can also lead to outbreaks and epidemics (Sanekata et al., 2003; Ahmed et al., 2004), whereas group C RV is less often observed causing sporadic diseases. Of the existing 10 G and eight P RV group A serotypes, G1 to 4, P[4] and P[8] are the most commonly observed, with G1P[8], G2P[4], G3P[8], and G4P[8] being the most common combinations recorded (Kostouros et al., 2003; Clark and Mckendrick, 2004).

Studies of T cell responses to RV infection in humans have reported that most healthy adults and children have circulating RV-specific T cells, with approximately 50% of RV-$CD4^+$ T cells expressing the intestinal homing receptor $\alpha4\beta7$, and with circulating RV-$CD4^+$ and RV-$CD8^+$ T cells secreting IFN-γ or interleukin (IL)-2 (Makela et al., 2004; Offit et al., 1992; Yasukawa et al., 1990; Rott et al., 1997; Parra et al., 2014). Frequencies of circulating IFN-γ^+ RV T cells are comparable to those specific for other mucosal respiratory viruses (Mesa et al., 2007), but these often possess profiles of terminally differentiated effector cells that are usually associated to those unable to provide long-term immunity (Parra et al., 2014).

Two live attenuated RV vaccines, Rotarix (GlaxoSmithKline) and RotaTeq (Merck), are licensed for global administration to pediatric populations. Rotarix contains a single G1P[8] human RV strain, whereas RotaTeq contains five RV strains, G1P7[5], G2P7[5], G3P7[5], G4P7[5], and G6P1A[8] (Yen et al., 2014). As in the case of natural neonatal RV infection, fair protection rates are achieved via humoral immunity using these vaccines. Though these are unable to protect against RV reinfection, they do offer protection against severe associated clinical symptoms causing patient hospitalization. These vaccines offer both homotypic and heterotypic immunity, and protection often correlates with increases in RV type–specific IgG or IgA antibodies, reviewed in Desselberger and Huppertz (2011). Although RV vaccine–induced humoral immunity substantially decreases disease burden, these vaccination strategies are less effective and difficult to implement in low-income countries requiring them most (Patel et al., 2012). As with natural RV infection, vaccines provide nonsterilizing immunity to children (Angel et al., 2007), where lack of establishment of long-term immunity against RV causes half of children's guardians to be at risk of becoming infected and presenting with severe associated disorders (Rodriguez et al., 1987). This further demonstrates that RV-specific T (RV-T) cells are crucial for the development of overall, long-term, protective immunity against RV (Franco et al., 2006; Offit et al., 1993). Indeed, in models of RV infection, vaccine-induced protective immune responses are dependent on antiviral cytokine production and by direct killing of RV-infected cells by T cell and B cell adaptive immune subsets (Jiang et al., 2008; Wen et al., 2016). In addition, with observations that gut $CD4^+$ T cells may become tolerogenic or anergic in response to RV infection, stimulating T cells with RV antigen in the presence of IL-2, IL-12, or R59949, a pharmacological diacylglycerol kinase alpha inhibitor, causes increased PBMC frequencies of RV antigen-specific T effector cells, including RV-$CD4^+$ TNF-α^+, RV-$CD4^+$ IFN-γ^+, and RV-$CD8^+$ IFN-γ^+ cells (Parra et al., 2014).

3.2 Viral Gastroenteritis Disorders and Adaptive Immune Responses Summary

Diarrheal disorders cause an annual 4–6 million deaths worldwide. RV is the leading cause of severe diarrhea outbreaks in infant and geriatric populations, with global annual estimates of 453,000 deaths in developing countries and 2.3 million pediatric hospitalizations. Most immunocompetent individuals have circulating RV-specific CTLs at comparable frequencies

to those elicited by other respiratory viruses, but which have terminally differentiated effector profiles rendering them incapable of conferring long-term protection against the reoccurrence of associated disorders. RV vaccine—mediated protection from severe disorders is from humoral non-sterilizing immunity unable to protect against reinfection, yet vaccination programs are challenging to implement in countries requiring them the most. RV-specific T cells are key to long-term protection, and vaccine-induced protection is dependent on cytokine production and direct killing of infected cells by T cells. Countermeasures against crucial helper $CD4^+$ T cell—developing anergic states may assist the development of vaccines conferring long-term protection.

4. EXANTHEMATOUS VIRAL DISORDERS

An exanthem is a widespread eruptive skin rash that may be associated with fever or other systemic symptoms. More than 50 infectious agents causing exanthems have been identified (Cherry, 1983), where more than 70% of recorded cases of combined fever and widespread rash in pediatric populations were caused by viral infections, relative to the 20% resulting from bacterial infections (Goodyear, Laidler, Price, Kenny and Harper, 1991). Correct diagnosis of these skin manifestations, resulting from direct inoculation of the infectious agent onto the cutaneous surface, or by dissemination from a distant site, is a main research theme on viral exanthems. This is because, while infections by many viral (i.e., paraviral) exanthems are benign and resolve spontaneously, others may rapidly lead to fatal conditions, reviewed in Drago et al. (2017). Thus, special attention in diagnosing even vaccine-preventable viral exanthems must be applied to avoid the arising of serious complications in nonimmune pregnant women and their fetuses from the more harmful classes of viruses causing exanthems (White et al., 2012).

Common exanthematous infections are typically caused by transmission of viruses from person-to-person (with exception of alphaviruses having a mosquito vector), and where a multitude of viruses are their causative agents, including rubeola virus, rubella virus, human parvovirus B19, human herpesvirus (HHV) type 6, varicella-zoster virus (VZV), variola, alphaviruses, and molluscum contagiosum virus (Table 1). Numerous other exanthematous disorder causing viruses are not covered in this section, including Ebola and Zika, but which are becoming classified as emerging viral

exanthems due to the increasing numbers of at-risk populations and the critical need to classify these diseases to minimize outbreaks and risk to pregnant women and fetuses (Keighley et al., 2015).

4.1 Rubeola Virus Classification, Epidemiology, Immunology, and Vaccinology

Rubeola, or measles virus (MeV), belonging to the morbillivirus genus of the Paramyxoviridae family, is a negative-sense RNA virus having a nonsegmented genome and a lipid envelope, and measuring up to 250 nm in diameter, reviewed in Griffin et al. (2012). The 16 kb genome encodes eight proteins: the viral envelope is composed of hemagglutinin (H) and fusion (F) GPs projecting from the matrix (M) protein lining its interior. The helical nucleocapsid is composed of the RNA and nucleocapsid (N) protein packed within the envelope as a coil with the phosphoprotein (P) and large polymerase (L) proteins attached. The two NS proteins, C and V, regulate cellular response to infection and modulate IFN signaling (Bellini et al., 1985).

Humans are the only natural host of highly contagious MeV virus spread by the respiratory route. Despite the availability of a safe and efficacious vaccine, measles remains one of the most important viruses causing child morbidity and mortality worldwide (Moss and Griffin, 2006; Wolfson et al., 2009). Infection by MeV is associated with up to 10% of mortality rates in African children (Grais et al., 2007; Nandy et al., 2006), and with 25% in unvaccinated refugee camp and virus-naive population mortalities (Moss, 2007; Shanks et al., 2011). Female mortality is a dominant feature disorders resulting from infection (Garenne, 1994), and many acute mortalities from secondary infections resulting from immune suppression induced by MeV are also observed (Beckford et al., 1985). MeV has a persistent and long latency infection period, often resulting in the development of subacute sclerosing panencephalitis (SSPE) in males, causing fatal neurologic disease presenting itself many years following the original infection (Bellini et al., 2005).

Adaptive cellular immune responses are generally regarded as most important for clearance of MeV. Children with low plasma Ig may recover from MeV infection, while those with defects in cellular immunity develop progressive infections (Albertyn et al., 2011; Mcquaid et al., 1998). MeV-specific antibody and T cell responses coincide with the onset of the rash, whereby rash biopsies of MeV-replicating, infected epithelial cells, have high levels of $CD4^+$ and $CD8^+$ T cell infiltrates (Polack et al., 1999).

$CD8^+$ T cell subsets appear to be particularly important for control and clearance of infectious MeV, where expanded circulating virus-specific CTLs are found in the blood of patients suffering rash, and increases in $CD8^+$ T cells are also found in MeV-induced pneumonias (Jaye et al., 1998; Mongkolsapaya et al., 1999; Myou et al., 1993). In addition, depending on the target tissue and cell type analyzed with regards to MeV infection, though differentially rated, both cytotoxicity and IFN production have been implicated as key effector mechanisms for MeV clearance (Patterson et al., 2002; Stubblefield Park et al., 2011; Finke et al., 1995), with specific combinations of $CD4^+$ T cells, $CD8^+$ T cells, and B cells recorded as required for the control of primary MeV infection (Tishon et al., 2006).

Protection against measles is based on MeV-specific humoral, antibody-based, immunity. Diagnostically, the current gold standard of protection is via quantification of neutralizing antibodies against the viral hemagglutinin (H) and fusion (F) surface GPs (Bouche et al., 2002; Haralambieva et al., 2011; Plotkin, 2010). MeV, however, triggers an aggressive immune response, involving both the humoral and cellular arms of the immune system (Moss and Griffin, 2012; De Vries et al., 2012; Buchanan and Bonthius, 2012). Once measles has been cleared, it is memory T cells that can provide lifelong immunity against reinfection by MeV (Bester, 2016). Importantly, during MeV infection, immune reactions to other pathogens are suppressed from weeks to years, leading to risk and susceptibility to secondary infections, and which is believed to be a driver of complications and mortality long after measles had been cleared. Conversely, this measles-induced immune "amnesia," sometimes disabling immune memory for up to 3 years, has been suggested to work toward herd protection against other infections and is supported by the association of measles vaccination with lowered mortality rates from other childhood infections (Mina et al., 2015). Occasional spontaneous tumor regressions have also been observed to occur during natural measles infection, suggesting that MeV infection may be adopted in the generation of safe and effective oncolytic viruses (Russell and Peng, 2009).

4.2 Rubella Virus Classification, Epidemiology, Immunology, and Vaccinology

Rubella virus belongs to the Togaviridae family and is the sole member of the *Rubivirus* genus. Rubella contains a single-stranded, positive-sense RNA genome (Frey, 1994), and its viral particles measure between 50 and 85 nm in diameter (Oshiro et al., 1969) and have a pleomorphic

nucleocapsid surrounded by a host-derived lipid membrane (Battisti et al., 2012). The E1 and E2 rubella protein spikes are anchored to the external layer of the membrane, with membrane-bound E2 proteins bridging rows of E1 proteins, considered as the main immunodominant antigens responsible for controlling receptor-mediated endocytosis (Petruzziello et al., 1996; Katow and Sugiura, 1985). Antibody levels against the neutralizing domain of E1 correlate with protection against rubella virus (Mitchell et al., 1996; Cordoba et al., 2000; Wilson et al., 2006).

Rubella virus is spread from person-to-person via the respiratory route and is the causative agent of rubella disease, commonly known as German measles (Lambert et al., 2015). Although rarer in the United States, rubella infection remains a major health concern in developing countries (Tosh et al., 2009). Although acquired rubella infection is not severe in adults, transplacental transfer of the virus to the developing fetus during maternal viremia can cause devastating consequences of congenital rubella syndrome (CRS) (Watson et al., 1998), where more than 100,000 infants worldwide are born with CRS each year (Robertson et al., 2003). Common CRS symptoms include spontaneous abortion, premature delivery, fetal death, ocular abnormalities, neurological problems, abnormal cardiac development, and deafness (White et al., 2012). Congenital malformations due to CRS may be present at birth, while other conditions such as diabetes mellitus, deafness, intellectual disability, and/or subacute encephalitis may develop months to years later (Watson et al., 1998; White et al., 2012).

From mass immunization programs, the number of rubella cases has progressively declined and was no longer endemic in the United States as of 2004 but remains endemic in other countries, with a dramatic increase in reported cases the last decade (Reef et al., 2011). Recently, Africa and Asian have seen 20-fold increases in rubella cases, representing a significant proportion of the over 121,000 global cases reported, but where neither of these regions has immunization policies in place to control rubella outbreaks (White et al., 2012). A recent, 2013 rubella epidemic in Japan reporting over 11,000 cases, with at least 13 CRS cases (Minakami et al., 2014), has also served to demonstrate that partial vaccination strategies can lead to major outbreaks. In this case, vaccination was only provided to young women, while outbreaks affected the adult male populations—a phenomenon which has also been observed in other countries applying such vaccination strategies (Paradowska-Stankiewicz et al., 2013; Janta et al., 2012).

Once measles is cleared, memory T cells can provide lifelong immunity to MeV (Bester, 2016), and distinct patterns of cellular immunity to rubella

virus are observed and related to the time elapsed following vaccination (Lambert et al., 2015). Predominant biomarkers of early cellular measles immunity are characterized by an immunosuppressive phenotype, with increases in IL-10 and TNF-α and decreases in IFN-γ and proliferative properties of circulating peripheral lymphocytes (Pukhalsky et al., 2003). Late immunity is shifted to predominantly proinflammatory cytokine profiles via increased concentrations of IL-6, granulocyte-macrophage colony-stimulating factor, and TNF-α, in combination with decreases in IL-10 (Dhiman et al., 2010). Human leukocyte antigens (HLAs), known to play critical roles in immune response to viruses, contribute to the heterogeneity of the immune response to rubella virus as a result of their polymorphic nature, whereby HLA class I and II polymorphisms restrict the available repertoire of rubella antigens presented to T cells and therefore influence the subsequent immune response (Mitchell et al., 1996; Ou et al., 1994, 1998). Current efforts are placed on deciphering the immunogenetics of antirubella humoral and cell-mediated immune responses, with a focus on better understanding HLA polymorphisms toward the development of vaccine candidates that utilize constructs comprised of HLA-specific epitopes that can induce immunity across heterogenetic populations, reviewed in Lambert et al. (2015). Both natural infection and vaccines induce humoral and cellular immune responses conferring protection against rubella (Tosh et al., 2009). While humoral responses have been conventionally used to measure and record protective immunity in human populations, cellular immune responses are intrinsic to humoral immunity (Bautista-Lopez et al., 2000; Horstmann et al., 1985; Ovsyannikova et al., 2004; Nepom et al., 1997; Vesikari et al., 1975; Akaboshi et al., 2001; Farzaneh et al., 2003).

Since its induction into healthcare systems, immunization with live attenuated rubella virus vaccine has been demonstrated to be safe and effective at preventing infection, CRS, and to interrupt endemic rubella transmission (Lambert et al., 2015). The live attenuated rubella vaccine strain RA27/3 has a proven track record for safety and immunogenicity efficacy (Hilleman et al., 1968; Plotkin, 1979), where single doses have been demonstrated to potently induce humoral immunity and lifelong protection against infection, and where the vaccine has also been demonstrated to boost previously immunized persons (Diaz-Ortega et al., 2014). From their safety and efficacy, use of recombinant rubella vectors has also been tested toward enhancing immune responses against SIV and HIV epitopes, where increases in memory B cell repertoires have been observed upon re-exposure to

rubella vectors (Virnik et al., 2013). Durable HIV-specific cellular immunity has been observed from rubella vector boosting, with cytotoxic antigen-specific responses by central and effector memory $CD4^+$ and $CD8^+$ T cell subsets (Rosati et al., 2015).

4.3 VZV Classification, Epidemiology, Immunology, and Vaccinology

VZV, also known as HHV-3, is a virus of the *Varicellovirus* genus from the Herpesviridae family. Humans are its only vector (Hambleton and Gershon, 2005), where it specifically infects T cells, epithelial cells, and ganglia (Gershon et al., 2015). VZV viruses have diameters measuring up to 200 nm and are encoded by a linear double-stranded DNA genome consisting of approximately 125 kb and encoding at least 70 unique genes, with all but the exception of 6, having homologs in herpes simplex virus (Cohen, 2010). VZV virions are composed of the viral DNA, the capsid, the tegument surrounding the capsid, and the envelope surrounding the tegument and which incorporates the major viral GPs (Arvin, 1996). During lytic infection phases, VZV produces at least 12 GPs expressed on both virions and human cell surfaces. During this process, and which is common to other herpesviruses, gene expression is believed to proceed in an orderly cascade of immediate early genes, early genes, and late genes. During latent VZV infection, gene expression is restricted until reactivation for additional rounds of lytic infection (Gershon and Gershon, 2010).

VZV has extraordinarily high transmission rates and is highly communicable via the airborne transmission route, with concentrated virus coming from vesicles shedding from skin lesions, leading to cell-free contagious airborne viruses, and as evidenced by the fact that infected children without skin lesions are not contagious (Tsolia et al., 1990; Chen et al., 2004). Primary VZV infection causes varicella, also commonly known as chickenpox. As cellular immunity to VZV wanes in the elderly and immunocompromised populations, latent VZV becomes reactivated and causes zoster (i.e., shingles, herpes zoster), which is usually associated with chronic pain but also numerous other serious neurological and ocular disorders, as well as multiple visceral and gastrointestinal disorders, including ulcers, hepatitis, and pancreatitis (Gershon et al., 2015; Gilden et al., 2010). Available antiviral drugs and vaccines against varicella and zoster are safe and effective for treatment and prevention strategies (Gershon and Gershon, 2010).

Varicella is globally endemic and is transmitted year-round, with frequent epidemics occurring every 2 to 3 years. Outbreaks most commonly

occur in nurseries and schools, in hospitals and other medical institutions, and in refugee camps and military and correctional facilities (Izurieta et al., 1997; Levy et al., 2003; Longfield et al., 1990). Although it can often be a self-limiting disease, varicella can also result in death, where in developed countries, an estimated 5 of 1000 patients are hospitalized with serious complications, with up to three deaths per 100,000 patients (Galil et al., 2002; Rawson et al., 2001). Complications from varicella requiring hospitalization include bacterial superinfections of the skin, blood, bones, and lungs, as well as encephalitis and hemorrhagic manifestations in pediatric and immunocompromised populations (Gershon et al., 2015). Importantly, acquiring VZV during early pregnancy often results in severe congenital defects in 1% of newborns (Enders, 1984). VZV is a great example of success through herd vaccination programs for children, dramatically influencing its epidemiology, and causing 95% declines of hospitalization cases in the United States (Gershon et al., 2015).

Following its transmission to the respiratory mucosa, VZV proliferates in the oral pharynx, where it infects human tonsillar activated memory $CD4^+$ T cells and induces their tissue-homing properties (Sen et al., 2014). VZV can be propagated to T cell–rich regional lymph nodes for rapid proliferation and is then disseminated by the circulation to infect dermis, epidermis, and other organs (Ku et al., 2002, 2004). Lymphopenia is typically observed in patients during viral incubation, followed by an increase in leukocyte counts, correlating with the onset of rash until the resolution of viremia. During infection, VZV can be recovered from PBMCs in children exhibiting rash (Ozaki et al., 1984; Koropchak et al., 1992; Sawyer et al., 1992), is extensively observed in thymic lymphocytes (Levin, 2014), and observed in all T cell subsets examined (Moffat et al., 1995). Though innate skin immunity can cause delays in multiplication of skin-bound VZV while the adaptive immune system mounts an attack, however, aggressive VZV replication in the skin results in characteristic varicella rash (Ku et al., 2004). High VZV titre-skin vesicles from rash provide cell-free virus for person-to-person transmission (Chen et al., 2004). VZV also latently infects neurons of cranial nerve ganglia, dorsal root ganglia, and enteric and autonomic ganglia (Gershon and Gershon, 2010). VZV reactivation causes ganglia to become necrotic and hemorrhagic (Head et al., 1997), with VZV proteins found in neurons and non-neuronal cells, and where this VZV-induced ganglionitis is often also marked by the upregulation of MHC class I and II proteins associated infiltration of $CD4^+$ and $CD8^+$ T cells (Schmidbauer et al., 1992; Steain et al., 2014; Gowrishankar et al., 2010).

Before VZV vaccines became available, approximately 30% of infected adults later developed shingles (Yawn et al., 2007). The single dose, lyophilized, live, attenuated VZV vaccine (i.e., zoster vaccine live (Zvl), Zostavax, Merck) is indicated for prevention of latent VZV reactivation leading to shingles in individuals older than 50 years. ZVL is licensed in over 55 countries, with 34 million distributed doses globally (Willis et al., 2017), and which has associated efficacy rates of over 50% in all ages tested (Oxman et al., 2005; Schmader et al., 2012); consistent with original clinical trial datasets (Tseng et al., 2011; Langan et al., 2013; Marin et al., 2015). However, increases in VZV susceptibility have arisen due to increasing aging populations, and in immune-suppressed organ transplant recipients, chemotherapy patients, HIV-infected individuals, and those suffering from chronic illnesses (Forbes et al., 2014). In these patients, earlier exposure to exogenous VZV protects against shingles by boosting cellular immunity (Arvin et al., 1983; Thomas et al., 2002).

The memory immune response following naturally acquired primary VZV infection is characterized by VZV IgG and IgA antibodies, as well as VZV-specific $CD4^+$ and $CD8^+$ T cells, where VZV-specific IgG antibodies bind many VZV proteins and mediate virus neutralization and antibody-dependent cytotoxicity, reviewed in Arvin (2008). The frequency of VZV-specific memory proliferating T cells is estimated to be approximately one in 40,000 PBMC (Hayward et al., 1986). VSV-specific memory cytotoxic MHC class I- or class II-restricted T cells producing IFN-γ and TNF-α can recognize the VZV gE, gB, gC, gH, gi, Ie62, and IE63 proteins and can be found to persist for over 20 years after varicella exposure (Jenkins et al., 1998; Huang et al., 1992; Asanuma et al., 2000; Diaz et al., 1989; Hayward et al., 1986; Sharp et al., 1992; Sadzot-Delvaux et al., 1997).

The ability of the live attenuated varicella vaccine to elicit VZV-specific IgG and T cell immunity in naive hosts was established during its prelicensing clinical evaluations (Gershon et al., 1992), and where, as expected from its design, the magnitude of these VZV-specific immune responses correlated with infectious virus content and with antigen content of individual vaccine formulations (Bergen et al., 1990; Watson et al., 1993). Importantly, it was later discovered that providing two doses to children resulted in higher IgG antibody titres and increased T cell proliferation and where experimental evidence suggesting that memory responses were sustained more effectively from such regimens (Watson, 2008). These observations led to the more recent recommendation of implementing of a two-dose regimen of varicella vaccine for all vaccine recipients (Arvin, 2008). Studies of how

regimens affect long-term protection by the adaptive T cell immune response to vaccination, as exemplified by VZV vaccination studies, have the potential to modify dosages and timelines to maximize overall and persisting beneficial long-term effects from vaccination against many other viruses.

4.4 Variola Virus Classification, Epidemiology, Immunology, and Vaccinology

Historically, smallpox was a severe human disease caused by the variola virus (VARV), which was both highly lethal and highly contagious prior to its eradication from human populations in 1980 (Moore et al., 2006). VARV belongs to the genus *Orthopoxvirus* of the family *Poxviridae*, which also includes zoonotic species: vaccinia virus (VACV), monkeypox virus, cowpox virus, and camelpox virus (Shchelkunov, 2013). Orthopoxviruses are enveloped, brick-shaped viruses measuring 350 by 270 nm, and containing a double-stranded DNA genomes encoding 150–200 genes, and measuring approximately 200 kb (Garon et al., 1978). Unlike other DNA viruses, these replicate as 'virus factories' in the cytoplasm of infected cells (Pauli et al., 2010). VARV encodes approximately 200 proteins, where over 80 of these are found at terminal regions of the genome and are associated with host immune evasion.

The origin of smallpox is unknown, but VARV is considered to be one of the most deadly diseases of human history, decimating populations to such an extent that it significantly altered the course of human civilizations. Smallpox is believed to have first appeared in 10,000 BC in Africa, with the oldest credible confirmation found in Sanskrit writings from 1500 BC and where smallpox lesions are believed to be observed on the mummified Egyptian ruler Ramses V (1100 BC) (Ristanovic et al., 2016). Prior to its eradication in 1980, VARV circulated in the human population for many centuries and repeatedly caused large-scale epidemics. In the 18th century for instance, smallpox caused the death of more than 400,000 Europeans per year (Babkin and Babkina, 2015; Smith and Mcfadden, 2002).

Despite VARV eradication from the human population more than two decades ago, fears about its potential re-emergence or the threat of its use as a potential bioterrorism agent have not subsided. This has led to numerous debates concerning the destruction of existing viral stocks, currently maintained in the United States and Russia. Destruction of these stocks has been postponed for the benefit of further research elucidating VARV mechanisms of pathogenesis toward the design of therapeutics as well as on efficacious

vaccine strategies that may be required for potential future outbreak (Smith and Mcfadden, 2002; Stone, 2002).

Immune-evasion mechanisms by VARV are the least understood among the orthopoxviruses due to difficulties of finding an appropriate host animal model (Turner and Moyer, 2002), along with limited availability of authentic variola proteins since its eradication (Massung et al., 1993). Thus only two variola proteins, namely smallpox inhibitor of complement enzymes (SPICE) and vaccinia virus complement control protein (VCP), have been characterized and are similar in structure (Dunlop et al., 2003). These viral antigens regulate the human complement system (Yadav et al., 2008), are important for stimulating innate immunity, and also have important features for adaptive immunity, shown to bolster antiviral T cell responses including IFN and cytokine expression (Noris and Remuzzi, 2013; Moss and Shisler, 2001).

VACV has been used more extensively for human immunization than any other vaccine and what was employed to provide cross-protection against VARV toward smallpox eradication (Jacobs et al., 2009). The first generation VACV/VARV vaccines produced in the 1970s and 1980s (Dryvax, Apsv, Lancy—Vaxina, L-IVP) contained live VACV (Kennedy et al., 2009), and induced robust humoral immunity is characterized by high antibody titers, neutralizing and opsonizing viral particles, fixing complement, hemagglutination, and antibody-dependent cell cytotoxicity (Amanna et al., 2006; Panchanathan et al., 2008). These vaccines have since been observed to generate adaptive immune responses over many concentrations (Frey et al., 2002; Rock et al., 2006), including the secretion of effector cytokines (e.g., IFN-γ) and the lysing of infected cells (Amanna et al., 2006; Hammarlund et al., 2003). Most second-generation vaccines created for biodefense contain replication competent viruses (Artenstein and Grabenstein, 2008) and have comparable efficacies to Dryvax. Third-generation vaccine formulations using attenuated VACV strains (LC16m8, Mva, Nyvac, dVVL) have increased safety profiles (Artenstein, 2008; Kennedy et al., 2009). Proof that adaptive cellular immunity is essential in preventing the spread of VARV following immunization and in its generating overall protective immunity against smallpox comes from observations that individuals having T cell—deficiency disorders suffered serious and sometimes fatal infections after vaccination, but that agammaglobulinemic children were not at risk of these adverse complications (Rock et al., 2006).

VARV vaccine induces strong $CD4^+$ and $CD8^+$ T cell responses, peaking after immunization and then contracting to provide stable memory T

cell populations that remain detectable for decades (Amanna et al., 2006; Hammarlund et al., 2003) and with memory $CD4^+$ T cells persisting the longest (Amara et al., 2004). Defects in cellular immunity lead to uncontrolled vaccinia infection (Lane et al., 1970), where $CD4^+$ and $CD8^+$ T cells are able to prevent mortality of B cell–deficient animals infected with VACV (Belyakov et al., 2003) and where $CD4^+$ T cells have the most protective overall effects (Xu et al., 2004), and are essential for optimal CTL function and memory formation (Sun and Bevan, 2003; Kennedy et al., 2009). VACV-specific $CD4^+$ and $CD8^+$ T cells recognize a diverse array of viral proteins, and $CD8^+$ T cell epitopes are predominantly found in early, non-structural genes and transcription factors (Terajima et al., 2008). $CD4^+$ T cell epitopes are from late viral products including membrane, structural proteins, and replicative enzymes (Jing et al., 2008), and linkage of B cell and $CD4^+$ T cell epitopes to VARV proteins suggests T helper cell–B cell interactions are those required for generation of robust VACV-specific antibody responses (Sette et al., 2008). In humans, VARV-specific $CD4^+$ and $CD8^+$ T cells have been observed to persist for over 75 years following immunization (Rock et al., 2006).

4.5 Exanthematous Viral Disorders and Adaptive Immune Responses Summary

Exanthem disorders by viruses represent more than 70% of cases of combined fever and widespread rash in pediatric populations, and their correct diagnosis is especially critical for the distinguishing of benign versus lethal viral strain variations that can cause lifelong morbidities in children born from infected mothers. MeV is transmitted via human respiratory routes, and despite vaccine availability, still causes 10% of African children mortalities, and severe risk of SSPE-derived fatalities years later in survivors. Historically, in common with many other viruses, the gold standard diagnostic of protection is made by quantification of humoral neutralizing antibodies. Adaptive cellular immune responses are, however, those most critical for MeV clearance, where MeV-specific T cell responses coincide with rashes densely infiltrated by $CD4^+$ and $CD8^+$ T cells. Combinations of $CD4^+$ T cells, $CD8^+$ T cells, and B cells control primary infection, where $CD8^+$ T cells dominate for control and clearance, and memory T cells are able to provide lifelong protection. MeV infection induces general long-term immunosuppression leading to vulnerability to other pathogens causing secondary infections, but this immunosuppression is believed, by

some, to be simultaneously conferring herd protection and have been observed to induce spontaneous tumor regression.

Rubella virus infection has progressively declined from immunization programs but continues to be endemic in many countries, as a result of complete absence of or problematic or partial vaccination programs, still causing severe CRS cases in 100,000 infants worldwide, per year. While humoral responses are conventionally used to measure protective immunity, it is adaptive immunity that confers protection. Both natural infection and vaccination induce humoral and cellular immune responses, where memory T cells can provide lifelong immunity, with presence of cytolytic T cell biomarkers from vaccine-induced immunogenicity. Vaccines in development can comprise HLA-specific epitopes inducing immunity across heterogenetic populations. Since rubella vaccines can boost the previously immunized, their vectors are being investigated for use toward immunization programs for unrelated viruses.

VZV has extraordinarily high human transmission rates. Primary VZV infection causes varicella, and before vaccination programs were initiated, would re-emerge from declines in adaptive immunity to cause zoster in 30% of in immunocompromised populations to cause the hospitalization of 1 of every 200 and the death of three per 100,000 patients. VZV represents a poster child of herd vaccination programs that led to 95% declines in hospitalization events. VZV infection rates are again on the rise in immunocompromised and immune-suppressed populations. It infects human tonsillar activated memory $CD4^+$ T cells that home to the lymph to then infect $CD4^+$ and $CD8^+$ T cells, followed by a lymphopenia resolved at rash onset. Innate immunity controls VZV spread until adaptive immunity develops to fully counter the infection. VSV-specific memory CTLs persist 20 years after varicella exposure, and observations that increased T cell proliferation with better-sustained memory responses result from multiple booster doses of vaccine have caused modifications in vaccination programs.

Smallpox by VARV was one of the most deadly diseases in human history, causing more than 400,000 European casualties annually prior to its vaccine-mediated eradication. Viral stocks are maintained from the necessity of developing new vaccines to counter potential future re-emergence of VARV from natural- or bioterrorism-derived sources. Characterized variola proteins amplify and strengthen T cell responses. First-generation VACV vaccine induced robust humoral immunity and ADCC, in addition to generating adaptive immune responses marked by cytokines and cell lysis. VARV vaccine induces strong initial effector $CD4^+$ and $CD8^+$ T cell

responses having B cell linkage, then contacting to generate stable memory populations of VARV-specific $CD4^+$ and $CD8^+$ T cells that can persist for over 75 years. Accordingly, second- and third-generation vaccines created for biodefense are designed to stimulate adaptive cellular immunity.

5. HEPATIC VIRAL DISORDERS

Globally, liver cancer is the fifth most common of cancers, with an average of 374,000 cases per year, representing 7.2% of all cancers, and with mortality rates reflecting geographic incidence rates. Almost 85% of liver cancers occur in developing countries, with over 20 of 100,000 individuals affected by these diseases. Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and approximately 80% of cases are associated with chronic infection by hepatitis B virus (HBV) or hepatitis C virus (HCV) (El-Serag, 2012). Hepatitis viruses are so named because they display hepatotropism by preferentially infecting hepatocytes to cause liver inflammation, also known as viral hepatitis. Infection by HBV and HCV promotes liver cirrhosis in most affected, leading to the development of HCC in up to 30% of patients (Fattovich et al., 2004). Approximately 5% of the global population (350–400 million people) are chronically infected with HBV and strong correlations between HBV prevalence and HCC incidence and mortality. Chronic HBV infection accounts for approximately 50% of HCC cases in adults and for all HCC cases in children (El-Serag, 2012).

Hepatitis transmission is from person-to-person contact with infected blood or body secretions or by the fecal-oral route and involving at least five specific viruses, namely hepatitis A, B, C, D, and E viruses (Table 1). Infectious viral hepatitis is an important challenge to health worldwide: hepatitis A virus (HAV) and hepatitis E virus (HEV) are acute and endemic in many low-income countries, usually causing self-limiting hepatitis, whereas HBC and HCV also cause acute illness but usually lead to chronic and progressive liver fibrosis, cirrhosis, and an increased risk of HCC (Stanaway et al., 2016). HBV is controlled in adults but is chronically persistent from neonatal infection (Shin et al., 2016).

5.1 Hepatitis Virus Classification, Epidemiology, Immunology, and Vaccinology

Hepatitis viruses differ in their virology. HBV is an enveloped DNA virus that belongs to the *Hepadnaviridae* family. It contains a 3200 bp, partially double-stranded relaxed-circular DNA genome that is reverse transcribed

via a pregenomic RNA intermediate and encodes four overlapping open reading frames, which are translated to produce viral core protein, surface proteins, reverse transcriptase, and HBx (Nguyen et al., 2008). Transmission of HBV results from exposure to infectious blood or body fluids containing blood, and HBV can integrate into the human genome, contributing to its genomic instability and ultimately to HCC (Zhao et al., 2016).

HCV is also transmitted by infected blood; but unlike HBV, HCV does not integrate into the host genome (Lin et al., 2015). HCV is also a positive-stranded RNA virus but is classified in the *Hepacivirus* genus within the *Flaviviridae* family. Its genome is 9.6 kb in length, includes an internal ribosome entry site, and encodes structural and NS proteins. The structural proteins form the viral particle and include the core protein and the envelope GPs E1 and E2. The NS proteins include the p7 ion channel, the NS2-3 protease, the NS3 serine protease and RNA helicase, the NS4A polypeptide, the NS4B and NS5A proteins, and the NS5B RNA-dependent RNA polymerase (Moradpour et al., 2007).

Hepatitis D virus (HDV) is also transmitted by contact with infected blood or other body fluids. HDV is an enveloped, negative sense, single-stranded, closed circular RNA virus, and requires HBV coinfection for its propagation, where infection with both viruses commonly results in severe liver pathologies. HDV genomic RNA of HDV is composed of approximately 1700 bp, packaged with approximately 200 molecules of hepatitis delta antigen to form viral particles. HDV envelope surrounding its genome and HDAg protein is composed of the three HBV small, medium, and large HBV HBsAg envelope proteins. HDV also does not encode its own replicase or polymerase, and rather utilizes host cellular machineries for its replication (Abbas and Afzal, 2013).

HAV and HEV are positive-stranded nonenveloped RNA viruses transmitted via the fecal-oral route, and unlike chronically persisting HBV and HCV, are typically cleared after acute infection of immunocompetent individuals (Park and Rehermann, 2014). HAV is a hepatotropic virus belonging to the *Hepatovirus* genus within the *Picornaviridae* family. Its genome consists of approximately 7500 bp and encompasses a single open reading frame coding for a single polyprotein, which is post-translationally processed into structural and NS proteins. The structural proteins of HAV are divided into the polypeptides VP1, VP2, VP3, and VP4, forming the icosahedral capsid of the virus. NS proteins 2B, 2C, 3A, 3B, 3C, and 3D are involved in RNA replication and viral polyprotein processing (Martin and Lemon, 2006). HEV of the family *Hepeviridae* and genus *Orthohepevirus*

has a 7.2 kb genome having three opening reading frames encoding for the viral replicase, the capsid protein, and a small phosphoprotein required for the secretion of viral particles (Debing et al., 2016).

HAV and HEV are waterborne viruses that usually cause acute hepatitis without progressing to chronic liver disease (Joon et al., 2015), where annually, over 100 million cases of HAV and 28 million cases of HEV infections have been recorded globally (Makiala-Mandanda et al., 2017). HEV outbreaks are reported in Africa nearly every year, with some involving over 10,000 cases (Kim et al., 2014). HAV is highly endemic in Africa, infecting most children, conferring long-term immunity to reduce serious epidemics (Jacobsen, 2014). Hbv, Hcv, and HDV can be sexually, parenterally, or vertically transmitted and usually evolve into chronic hepatitis, liver cirrhosis, and HCC causing high morbidity and mortality rates, where globally, over 350 million people are chronically infected with HBV, 150 million with HCV, and 15 million with HDV (Kramvis and Kew, 2007; Hughes et al., 2011; Thursz and Fontanet, 2014). Superinfection of HBV patients with HDV frequently accelerates the progression of HBV disease to liver cirrhosis, considerably increasing the burden of chronic liver disease (Hughes et al., 2011).

HAV, HBV and HCV are responsible for the majority of viral hepatitis cases, and there are similarities and differences in immune responses to infections by these three viruses, possibly explaining the distinct disease courses and outcomes of each hepatitis virus infection (Shin et al., 2016). Type I and III IFNs, major components of the antiviral innate immune system, induce the expression of IFN-stimulated genes (ISGs), observed to be much more highly induced by HCV than HAV, and not at all by HBV, indicating that this virus is not recognized by the innate immune system (Su et al., 2002; Lanford et al., 2011; Wieland et al., 2004). Another component of the innate immune system, NK cells, are also believed to be responsible for protection against HCV, where increased NK cells in protected individuals coincide with increased IFN-γ and cytotoxicity (Shin et al., 2016).

Though virus-specific antibodies are produced by all viral hepatitis infections, these have differing roles according to the hepatitis virus infection. HAV-specific antibodies with virus-neutralizing activity are induced by natural infection and vaccine immunization and confer lifelong protective immunity (Walker et al., 2015; Martin and Lemon, 2006). HBV surface antigen HBsAg-specific antibodies are induced by infection and immunization with the recombinant protein and have

virus-neutralizing activity conferring protective immunity (Guidotti and Chisari, 2006). HCV-specific antibodies produced after infection do not offer long-term protection as these do not persist, are subject to loss of neutralizing activity from virus mutation, and are ineffective for cell-to-cell HCV transmission (Takaki et al., 2000; Dowd et al., 2009; Timpe et al., 2008).

T cells play critical roles during acute HCV and HBV infections, where robust and multiple epitope-specific $CD8^+$ T cell responses are assisted by $CD4^+$ T cells for spontaneous resolution of infection (Shin et al., 2016). This is supported by observations that the depletion of $CD4^+$ or $CD8^+$ T cells in chimpanzees delays rapid clearance and recovery from infection by these viruses (Grakoui et al., 2003; Thimme et al., 2003). When HCV and HBV infections become chronically persistent, virus-specific T cells become exhausted and functionally impaired. In acute HCV infection, virus-specific T cells are only detected in the blood and liver after 8 weeks postinfection, and their appearance coincides with large declines of virus titres (Thimme et al., 2002; Shin et al., 2006, 2011). HBV virus—specific T cell responses are also important for spontaneous resolution of HBV infection, where their responses are observed to be vigorous, broad, and polyclonal in patients resolving primary infections and where their absences are associated with prolonged infection and delayed viral clearance (Chisari et al., 2010; Thimme et al., 2003). $CD8^+$ T cells also play important roles in HAV infection, where these have been observed to target multiple epitopes of HAV, despite more recent results suggesting that HAV is controlled by virus-specific $CD4^+$ T cells and not $CD8^+$ T cells (Walker et al., 2015; Shin et al., 2016). Finally, hepatitis virus infection results in liver injury, not directly caused by these viruses but rather by immune-mediated mechanisms (Guidotti and Chisari, 2006). Liver injury biomarkers correlate with acute Hav, Hab, and HAC infection (Guidotti and Chisari, 2006; Park and Rehermann, 2014; Walker et al., 2015) and may result from cytotoxic activity of $CD8^+$ T cells, believed to induce apoptosis of hepatocytes in close proximity to their targeted cells (Guidotti and Chisari, 2006), by IL-22 producing Th17-differentiated T cells, and by recruitment of nonspecific mononuclear cells by HBV-specific cytokine secreting $CD8^+$ T cells (Iannacone et al., 2007; Shin et al., 2016).

Effective vaccines controlling HAV and HBV have been available for over 2 decades, and an HEV vaccine has also been licensed for use in China

since 2011 (Zhu et al., 2010; Stanaway et al., 2016). Neonatal HBV vaccination has proven to be highly effective in inducing protective antibodies and preventing perinatal and horizontal transmission of HBV (Lee et al., 1991). However, observations that HBsAg-specific IFN-γ- or IL-5-secreting PBMCs are absent in many adolescents suggest that booster vaccines should be administered to provide continued HBV immunization (Lu et al., 2008). HAV vaccination provides long-term immunity in the general population and in immunocompromised patients infected with HIV (Crum-Cianflone et al., 2011). There is no existing vaccine for HCV, despite ongoing efforts toward their design and testing for their ability to generate prolonged cellular and humoral immune responses, reviewed in Naderi et al. (2014). In the absence of a vaccine, progress in HCV treatment includes oral treatments achieving cure in most patients, including those previously considered as difficult to treat cases (Poordad et al., 2013; Lawitz et al., 2013).

5.2 Hepatic Viral Disorders and Adaptive Immune Responses Summary

Liver cancer is the fifth most common cancer, representing 7.2% of all cancers, with 374,000 annual cases from which 20 in 100,000 mortalities occur. HCC is the most common liver cancer, with 80% of cases resulting from chronic infection by HBV or HCV, with a significant 350 and 150 million chronically infected, respectively. In contrast, HAV and HEV cause acute hepatitis but do not progress to chronic liver diseases, and HDV infection depends on pre-existing HBV infection. HCV induces the expression of type I and III ISGs and NK cells, not at all present from HBV infection unrecognized by innate immunity. Virus-specific antibodies are produced by all viral hepatitis infections but have differing roles across infections. Robust and multiple epitope-specific $CD8^+$ T cell responses and dominant but depend on assistance from $CD4^+$ T cells for resolution of acute Hav, Hbv, and HCV infections. In chronic infections, cytolytic T cells either cause extensive liver injury to hepatocytes and/or become tolerant and functionally impaired. Effective vaccines controlling HAV and HBV provide protective antibodies. HAV vaccination provides long-term immunity to the immunocompromised, but booster vaccination programs are required for persistence of HBV immunization. No vaccine is licensed for highly variable and rapidly mutating HCV, despite numerous ongoing efforts to generate those which will provide robust cellular and humoral immune responses.

6. NEUROLOGIC VIRAL DISORDERS

Historically, the central nervous system (CNS) has been considered to be an immunologically privileged site within the body (Bailey et al., 2006; Galea et al., 2007; Engelhardt, 2008; Prendergast and Anderton, 2009). By definition, immunologically privileged sites, also including the brain, cornea, testis, and pregnant uterus, have a reduced or delayed ability to reject foreign tissue grafts compared with conventional sites within the body, such as skin (Streilein, 2003; Bailey et al., 2006; Carson et al., 2006; Mrass and Weninger, 2006; Kaplan and Niederkorn, 2007).

Though the CNS is protected by a highly complex barrier system, a wide variety of viruses still manage to gain access to it and induce diseases. Due to their sizes and tissue penetration strategies, the number of CNS viral infections outweigh bacterial, fungal, and protozoa CNS infections combined (Romero and Newland, 2003). Following CNS infection, inflammatory events can arise in distinct anatomical regions such as the meninges (meningitis), brain (encephalitis), and spinal cord (myelitis) or can also simultaneously arise in multiple regions (meningoencephalitis, encephalomyelitis). For many neurotropic viruses, viral cytopathology plays a major role in CNS dysfunction, reviewed in Swanson and Mcgavern (2015).

Virus can breach the protective barriers of the CNS in many ways, with the main route mechanism being via the blood, where inhaled or ingested viruses can move past the mucosa to establish infection in secondary lymphoid tissues and later be shed into circulating blood to cause broad systemic infections (Swanson and Mcgavern, 2015). The CNS parenchyma is protected from a plethora of agents carried in the circulation via an elaborate network called the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (Ransohoff et al., 2003). Viruses have evolved and adapted to overcome these barriers (Mcgavern and Kang, 2011), where some viruses can infect vascular endothelial cells, permitting direct passage across the BBB into the CNS (Verma et al., 2009; Moses et al., 1993; Coyne et al., 2007). In addition, parts of the CNS that are not completely protected by the BBB permit more rapid entry of several viruses (Van Den Pol et al., 1999; Wolinsky et al., 1974). Infected hematopoietic cells in circulating blood can also serve as "Trojan horses" that can transport undetected virus into the CNS (Clay et al., 2007; Tabor-Godwin et al., 2010). Other mechanisms can include systemic viral infections leading to massive systemic inflammation and an ensuing BBB breakdown which opens the floodgates

to CNS infection by a variety of otherwise restricted infectious agents (Arsenio-Nunes et al., 1975; Eugenin et al., 2006).

There are more than 30 recognized distinct virus strains that cause human neurological disease, and the majority of documented cases are caused by viruses that are transmitted to humans by blood-eating arthropod vectors, also known as arboviruses, that are mainly transmitted by mosquitoes and ticks and include polioviruses (PVs), alphaviruses, mosquito-borne flaviviruses, tick-borne orthobunyaviruses, mosquito-borne mammarenaviruses, and rabies virus (RABV; Table 1).

6.1 PV Classification, Epidemiology, Immunology, and Vaccinology

PV, the causative agent of poliomyelitis, more commonly referred to as polio, is a human enterovirus and member of the family of *Picornaviridae*. Typically spherical, nonenveloped picornaviruses range in diameter between 27 and 30 nm and have a positive-strand RNA of 7000—9000 nucleotides, translated into a polyprotein (i.e., VP4-VP2-VP3-VP1-2A-2B Poliovirus 2C-3A-3B-3C-3D), which yields 11 proteins upon its cleavage by viral proteases. Picornavirus replication occurs in the cytoplasm of infected cells in association with intracellular membranes, where virions are released by cell lysis, ultimately killing cells and causing extensive damage to tissues. The host immune response against picornaviruses includes cytokine release, antibody production, and CTL activation, reviewed in Dotzauer and Kraemer (2012).

The viral genome of PV is a single-stranded RNA of approximately 7500 nucleotides, enclosed in a nonenveloped capsid comprising 60 copies of four different polypeptides arranged with icosahedral symmetry (Racaniello, 2006). All three PV serotypes cause paralytic disease, and CD155 is the cellular receptor for all three serotypes, whereby PV interaction with CD155, expressed by many different cell types, leads to a conformational change of the virus particle and the following release of the RNA genome into the cellular cytoplasm (Mendelsohn et al., 1989; Hogle, 2002). Once in the cytoplasm, the viral RNA genome is translated, and the production of new infectious virions begins.

PV infection results from ingested virus that replicates in the oropharyngeal and intestinal mucosa (Sabin and Ward, 1941). From the primary sites of multiplication in the mucosa, PV virus drains into cervical and mesenteric lymph nodes and then into the blood, causing transient viremia symptoms. The person-to-person transmission of PV virus is through the fecal-oral

route. Once PV is shed in the feces, the majority of the natural human infection ends at this stage with a modest symptoms including sore throat, fever, and malaise (Dotzauer and Kraemer, 2012). However, in 1%–2% of PV-infected individuals, the virus gains entry to the CNS through neurons at neuromuscular junctions (NMJs) and replicates in motor neurons within the spinal cord, brain stem, or motor cortex and leads to the PV-characteristic flaccid muscle paralysis disorder poliomyelitis (Racaniello, 2006; Koyuncu et al., 2013). Approximately 10% of these paralytic cases result in death (Roush et al., 2007).

Following both PV infection and vaccination, neutralizing antibodies are generated to clear the virus, and these can be detected for many years, providing lifelong protection (Libbey and Fujinami, 2014). Vaccination with the injected inactivated PV vaccine prevents viral spread to the CNS, whereas vaccination with the live-attenuated oral PV vaccine protects against infection of the intestinal tract and also prevents person-to-person spread of the virus (Nathanson, 2008; Griffin, 2010). PV remains an important cause of neurologic disease as the three live-attenuated vaccine strains are at risk of recombining their genomes to revert to virulent form (Griffin, 2010). PV is endemic in Afghanistan, Pakistan, India, and Nigeria, where political reasons, in part, are the most significant modality toward achieving PV eradication via vaccination. PV can usually be cleared by the adaptive immune response. Under conditions of antibody deficiencies in humans, however, continuous fecal shedding of PV contributes to the establishment of persistent infection cycles (Martin, 2006; Nathanson, 2008; Libbey and Fujinami, 2014).

Though less is known about the roles of adaptive T cell responses in controlling PV infections relative to that of neutralizing antibody responses, it is known that PV-specific $CD4^+$ T cells are induced in vaccinated individuals, where key epitopes have also been identified (Graham et al., 1993; Simons et al., 1993). The induction of PV-specific $CD4^+$ T cells has been suggested to be the result of stimulating by PV-infected DCs and macrophages (Wahid et al., 2005; Dotzauer and Kraemer, 2012), where it has been demonstrated that HLA class II presentation remains intact in infected, antigen-presenting cells (APCs), and that cytolytic $CD4^+$ T cells produce IFN-γ to lyse PV-infected cells for virus clearance. PV-specific cytotoxic, IFN-γ-secreting cytotoxic $CD8^+$ T cell responses induced by infected macrophages have also been documented (Wahid et al., 2005), suggesting that both $CD4^+$ and $CD8^+$ cytolytic T cells partake in the adaptive immune reaction against PV (Dotzauer and Kraemer, 2012).

6.2 Flavivirus Classification, Epidemiology, Immunology, and Vaccinology

Approximately 73 viruses are included in the *Flavivirus* genus of the *Flaviviridae* family of viruses, with 40 of its species associated with dengue, yellow fever (YF), Japanese encephalitis (JE), tick-borne encephalitis, and West Nile encephalitis as the most important arboviruses causing extensive global morbidity and mortality (Diamond, 2003). Flaviviruses are enveloped viruses with single-stranded RNA genomes that are translated in the cytoplasm to generate a single polyprotein that is then cleaved into structural and NS proteins by virus and host proteases. The various encoded viral proteins assemble to generate the capsid, the envelope for receptor binding, membrane fusion and viral assembly, and the transmembrane proteins (prM) that assist in protein folding and function. The entry of flaviviruses into their target cells is mediated by the interaction of the E GP with host cell surface receptors (Perera-Lecoin et al., 2013).

Flaviviruses are believed to evade the immune system to enter the brain and spinal cord via circulating blood (Johnson and Mims, 1968), where these may cross the BBB by passive transport across the endothelium, by active replication in endothelial cells, or by a "Trojan horse" mechanism, where virus hides in inflammatory cells during their transit into the brain (Solomon and Vaughn, 2002). IFN-dependent and complement system innate immune responses, along with humoral neutralizing antibodies, protect against virus dissemination and spread, reviewed in Diamond (2003). Adaptive cellular immunity is also important toward the destruction of infected cells, whereby virus-specific CTLs become activated, proliferate, and release inflammatory cytokines following exposure to flavivirus-infected cells (Kesson et al., 1987; Kurane et al., 1989a; Liu et al., 1989; Murali-Krishna et al., 1996). There is also evidence that flavivirus replication is enhanced by myeloid cells, as observed for dengue, YF, West Nile, tick-borne, and JE viruses (Diamond, 2003).

The JE flavivirus is the leading cause of encephalitis and is amplified by waterfowl and only transmitted to humans by mosquito vectors, with no possibility of human-to-human transmission (Erlanger et al., 2009). Pediatric and geriatric populations are at higher risk of infection by JE (Burchard et al., 2009). While 99% of JE infections remain asymptomatic, JE can be devastating in symptomatic patients, causing mortality rates of 30% in these patient populations (Batchelor and Petersen, 2015). After approximately 14 days of JE incubation, these patients suffer from high fever, chills,

headache, myalgia, and confusion, where pediatric patients also have symptoms of gastrointestinal pain, vomiting, and seizures. Post-JE infection, handicaps from persistent neurological deficits can last a lifetime in up to 50% of these survivors. As there is no treatment against JE, the only method of prevention is avoidance of mosquitos and vaccination (Batchelor and Petersen, 2015).

The four available JE vaccines are registered worldwide and used in national immunization programs for different age groups, including inactivated Vero cell culture vaccine (JE-VC) (IXIARO), inactivated mouse brain–derived vaccine (JE-MB), a cell culture–derived (primary hamster kidney) live-attenuated vaccine based on the SA 14-14-2 strain manufactured in China, and a live-attenuated chimeric vaccine based on the genes of YF 17D backbone combined with Vero cell–propagated SA 14-14-2 strain (IMOJEV) (Chen et al., 2015). T cell responses to JE vaccination have been reported, where for SA14-14-2, T cell responses were detected in the majority following vaccination, and these cross-reacted with other flaviviruses (Turtle et al., 2017). JE-specific T cell responses are observed in PBMCs isolated from JE-infected patients and vaccinated individuals. $CD4^+$ and $CD8^+$ T cells directed against structural viral proteins were identified in vaccinated individuals, in contrast to specific $CD4^+$ and $CD8^+$ responses against NS or C proteins in infected patients (Nathanson and Cole, 1971). These findings indicate that NS proteins, and especially NS3 have important roles in the initiation of T cell responses, as the main target of JE-specific T cell–mediated immune responses. In addition, cytolytic $CD4^+$ T cells clones that cross-reactive with other flaviviruses have been generated from individuals immunized with inactivated JE vaccine (Aihara et al., 1998). Finally, $CD4^+$ and $CD8^+$ and Th1 T cells are believed to be primary determinants of protection from JE infection (Kumar et al., 2004a, 2004b).

6.3 Alphavirus Classification, Epidemiology, Immunology, and Vaccinology

Viruses from the Alphavirus genus are members of the Togaviridae family of viruses, a group of enveloped positive-sense RNA viruses. These are mosquito-borne viruses causing two major types of human disease. The Old World alphaviruses—Sindbis, chikungunya, and Ross River virus—cause arthritis and arthralgia, while the New World alphaviruses—eastern (EEEV), western (WEEV), and Venezuelan equine encephalitis virus (VEEV)—cause encephalitis (Trobaugh and Klimstra, 2017). Alphaviruses

are small, icosahedral-shaped, enveloped viruses and are approximately 70 nm diameter in size (Mancini et al., 2000; Morgan et al., 1961; Fuller, 1987). Alphavirus virions acquire host cell lipid membranes during viral assembly (Fuller, 1987; Acheson and Tamm, 1967; Vogel et al., 1986), with 80 E1 and E2 viral GPs spike protrusions, arranged in an icosahedral pattern embedded within their membranes and interacting with nucleocapsid (Fuller, 1987; Vogel et al., 1986; Owen and Kuhn, 1997). Alphavirus single-stranded, positive-sense, RNA genomes are 12 kb long and consist of two large open reading frames encoding the NS and structural polyproteins that are subsequently cleaved by both viral and host proteases to create four NS proteins (nsP1 to 4) and five structural proteins (C, E3, E2, 6k, E1) (Strauss et al., 1984; Hardy and Strauss, 1989); reviewed in Leung et al. (2011).

Of major concern are the New World EEEV, WEEV, and VEEV alphaviruses, which are naturally transmitted by mosquitos, but where VEEV is also highly infectious via the aerosol route (Zacks and Paessler, 2010). Precise mechanisms of entry of alphaviruses into the CNS remains elusive, however, once in, alphaviruses infect humans and equines neurons, causing neurologic symptoms from mild febrile illness to severe encephalitis resulting in death (Ramakrishna et al., 2002; Zacks and Paessler, 2010). Development of severe encephalitis is believed to result from neuronal cell death from accelerated viral spread and host neuroinflammatory viral responses (Paessler et al., 2006, 2007). Antibodies are protective against lethal meningoencephalitis when the virus is transmitted by insects, and virus-specific $CD4^+$ T cells are found to be important for protection from lethal meningoencephalitis from aerosol transmission routes (Paessler et al., 2007; Yun et al., 2009); reviewed in Libbey and Fujinami (2014).

VEEV remains an emerging disease threat by natural transmission as well as via its usage as a biological weapon. Of the New World alphaviruses, VEEV is the most important human and equine pathogen, it having caused outbreaks of febrile and neurological disease primarily in Latin America during the past century. Past outbreaks have lasted several years and have involved up to 100,000 equine and human cases over large geographical regions, with the largest outbreaks on record were from the 1960s, where central Colombia saw over 200,000 human cases and an estimated 100,000 equine deaths. More recent outbreaks in Mexico and South America are behind the classification of VEEV as a re-emerging disease (Weaver et al., 2004). Because VEEV can also be developed as a biological weapon amenable to use in warfare or terrorism, current global emphases on

biological defenses have renewed interest in its virology (Hawley and Eitzen, 2001; Weaver et al., 2004).

VEEV infection in humans typically causes nonlethal, incapacitating symptoms including fever, headache, malaise, myalgia, sore throat, and vomiting. Up to 4% of rarer cases of CNS involvement usually follow acute febrile phases, with associated severities of neurological disease ranging from somnolence and mild confusion, to seizures, ataxia, paralysis, and coma, with mortality rates ranging as high as 35% in infected children and 10% in infected adults (Bowen et al., 1976). VEEV has also been reported to cause long-term neurological deficits, abortions, and teratogenic effects (De La Monte et al., 1985; Rivas et al., 1997; Weaver et al., 1996). Like VEEV, though the majority of human infections with EEEV are asymptomatic, CNS involvement results in severe neurological signs, lesions, and sequelae, with an estimated associated human mortality rate of 75%, and with its neurological manifestations including facial edema, paresis, paralysis, respiratory impairment, altered mental state, and seizures in children, many of these symptoms persisting long-term in surviving patients. In fatal cases of EEEV, gross lesions in the brain include edema, meningeal congestion, hemorrhage, and malacia (Deresiewicz et al., 1997). As with VEEV and EEEV, natural human cases of WEEV typically show an early, flu-like illness with associated fever, malaise, and headache. Similar to EEEV, WEEV results in CNS involvement in a significant proportion of cases, including symptoms of somnolence, seizures, coma, and motor neuron dysfunction. Ninety percent of infants infected with WEEV have severe CNS symptoms (Calisher, 1994). Human mortality rates from WEEV infection range from 3% to 15%, and neurological sequelae may become permanent features in survivors (Steele and Twenhafel, 2010).

Alphavirus expression vectors based on Sindbis, Semliki Forest, and VEEV have been demonstrated to induce strong $CD8^+$ T cell responses against their antigens (Rayner et al., 2002; Lundstrom, 2002, 2003; Riezebos-Brilman et al., 2006; Schlesinger and Dubensky, 1999; Polo et al., 2000). Both innate and adaptive immune responses can control viruses targeting CNS neurons (Griffin, 2003). Viral disruption of the type I IFN signaling pathways interferes with survival from VEEV, as well as of those infected with Sindbis and West Nile viruses (Ryman et al., 2000; Samuel and Diamond, 2005; White et al., 2001). Virus-specific antibody responses are critical in limiting viral spread and facilitating clearance of infectious virus from neurons within the brain (Diamond et al., 2003; Levine et al., 1991). Both alpha beta ($\alpha\beta$) and gamma delta ($\gamma\delta$) T cell responses have been

demonstrated as being important for the control of VEEV (Paessler et al., 2006). T cell responses reduce mortality rates by direct killing of infected cells, producing antiviral cytokines and increasing production of virus-specific antibodies (Bilzer and Stitz, 1994; Patterson et al., 2002; Shrestha et al., 2006; Sitati and Diamond, 2006). VEEV replicon particles delivered as an adjuvant have been demonstrated to induce activation of $CD8^+$ T cell responses (Thompson et al., 2008). More recently, T cells have been demonstrated to facilitate recovery from VEEV-induced encephalomyelitis in absence of antibodies, responsible for dramatic reduction in viral titres in CNS, where $CD4^+$ T cells were the best T cell producers of IFN-γ response and were more efficient at controlling VEEV in CNS lesions than $CD8^+$ T cells, facilitating recovery from severe viral encephalomyelitis (Brooke et al., 2010).

Commercial equine vaccines marketed in the United States are generated with inactivated TC-83, which produces viremia, fever, and leukopenia in horses but generates robust neutralizing antibodies and VEEV protection from rechallenge (Walton et al., 1972). U.S. army special immunization programs provide inactivated C-84 to individuals failing to seroconvert in response to TC-83 boosters (Pittman et al., 1996); however, neither of these vaccines can be shown to completely protect nonhuman primates against aerosol exposure (Pratt et al., 1998). A more stably attenuated VEEV vaccine candidate called V3526 has been produced, where preclinical testing has demonstrated it to be safe and immunogenic and possibly superior to TC-83 (Pratt et al., 2003; Hart et al., 2000; Ludwig et al., 2001). Adaptive immune PBMC-derived biomarker signatures have been identified and able to efficiently stratify TC-83 vaccinated from naïve or nonresponding individuals (Erwin-Cohen et al., 2012).

6.4 RABV Classification, Epidemiology, Immunology, and Vaccinology

RABV is the type species of the genus *Lyssavirus*, within the Rhabdoviridae family. Rhabdoviruses are negative-sense, single-stranded RNA viruses having a distinctive bullet-shaped structure. Up to 10 viruses of Lyssaviruses have the potential to cause rabies in humans. These have a 12,000 nucleotide genome encoding five proteins: nucleoprotein (N), phosphoprotein (P), matrix (M), glycoprotein (G), and RNA-dependent-RNA polymerase (L) (Marston et al., 2007). RABV causes acute encephalitis in mammals, causing fatality rates of almost 100%. RABV commonly infects many animals, including bats, skunks, foxes, and dogs and can also infect insects and plants.

RABV in animal saliva spreads between hosts via bites or scratches. Infected animals can survive for years, secreting infectious particles in their saliva, but untreated infection in humans generally results in rapidly fatal acute myeloencephalitis (Koyuncu et al., 2013). Rabid dogs are the most important reservoirs for RABV, where dog bites account for more than 99% of human infections. RABV, like all members of Lyssaviruses, is neurotropic and infects peripheral nerves close to the primary site of the bite. RABV then rapidly moves by retrograde axonal transport to the dorsal root ganglia where virus replication begins (Johnson et al., 2010). RABV particles enter axons of motor neurons at the NMJ via their binding to nicotinic acetylcholine receptors (e.g., nAchR) and neural cell adhesion molecules (Ugolini, 2011). Transneuronal RABV spread occurs between synaptically connected neurons, whereby viruses move from postsynaptic to presynaptic neurons. In humans, a relatively long asymptomatic incubation period after initial RABV infection can occur, sometimes lasting up to 1 year, and providing some time for CNS infection intervention. However, death almost always ensues after RABV infection reaches the CNS, with marked behavioral and neurological symptoms (Koyuncu et al., 2013). Once RABV has entered the CNS, it rapidly moves to the brain and is associated with an explosive increase in virus replication. Initial symptoms include pain or paraesthesia close to the bite site and are often associated with fever, fatigue, and weakness in associated limbs. Nonspecific neurological symptoms including headache and anxiety occur days prior to acute encephalitis (Morrison and Wenzel, 1985). Currently, there are no available therapies against disease symptoms once they develop, and death ensues within a number of days following CNS-associated symptoms (Jackson et al., 2003) and reviewed in Johnson et al. (2010).

RABV replication begins following CNS penetration, thereby limiting earlier possible detection of low-level primary antigens in the peripheral circulation. This delays antigen presentation, where antigens later but rapidly drain from the CNS to local lymphoid tissues (Knopf et al., 1998). Once B cells are stimulated, the next delaying obstacle is re-entry into the CNS, but experimental models have demonstrated T and B cell infiltration of dorsal root ganglia, spinal cord, and brain (Johnson et al., 2008), with T cells as the major immune subsets, but where most of these CNS-infiltrated T cells have Fas-mediated apoptotic phenotypes (Baloul and Lafon, 2003). Further intrinsic complexities in immune responses are present in the CNS, including tight MHC expression regulation (Irwin et al., 1999), and the expression of immunosuppressive factors by neuronal cells. Additionally,

the BBB remains intact during RABV infection (Roy et al., 2007). Numerous studies have suggested that the virus suppresses the adaptive immune response, believed to be in part due to a deficit of adaptive immune effector cell accumulation within the CNS due to a virally induced reduction in BBB permeability (Libbey and Fujinami, 2014; Roy et al., 2007).

Two RABV vaccines are licensed for human application, the human diploid cell vaccine manufactured by Aventis Pasteur and the purified chick embryo cell vaccine manufactured by Chiron (Johnson et al., 2010). Pre-exposure vaccination given to healthcare personnel, laboratory workers, and travelers to endemic areas causes detectable IgM and IgG antibodies within a week following exposure, and long-term studies have provided evidence that IgG antibodies provide the most effective protection against RABV due to its ability to penetrate tissues, in contrast to IgM which cannot penetrate tissues (Turner, 1978). A multifaceted approach for human rabies eradication involving government support, disease awareness, and vaccination of at-risk humans and dogs will be required to achieve the goals of the World Health Organization in eradication of rabies by 2030 (Fooks et al., 2017).

6.5 Neurologic Viral Disorders and Adaptive Immune Responses Summary

The CNS is immunologically privileged and protected by a highly complex barrier system. Viruses that have evolved to overcome these barriers can cause CNS infections greatly outnumbering those from all bacterial, fungal, and protozoa infections combined. Ingested PV multiplies in the oropharyngeal and intestinal mucosa and drains to cervical and mesenteric lymph nodes and then into the blood ahead of penetrating the CNS to cause polio, with 10% of cases resulting in death. Both neutralizing antibodies and the adaptive immune system can clear PV infection and may provide lifelong protection. Vaccination combinations can induce PV-specific cytolytic $CD4^+$ and $CD8^+$ T cells for virus clearance, but their coadministration can pose the risk for reversion to virulence by recombination.

The JE flavivirus is amplified by waterfowl and transmitted to humans by mosquitoes, and while 99% of its infections are asymptomatic, mortality rates in 30% of infected individuals cause associated disorders that leave its survivors a lifetime of associated morbidities. As there is no existing JE treatment, prevention involves either avoidance of mosquitoes or vaccination. Flaviviruses evade the immune system to cross the BBB by an inflammatory cell—mediated "Trojan horse" mechanism. JE dissemination is limited by innate

immune responses, neutralizing antibodies produced by humoral immunity, and by virus-specific CTLs. JE vaccines are licensed worldwide, and the majority of vaccinated individuals have circulating JE-specific $CD4^+$ and $CD8^+$ T cells that can cross-react with other flaviviruses.

Alphaviruses are transmitted by mosquito bites to infect neurons, causing mild to severe encephalitis resulting in death, with past outbreaks numbering in the hundreds of thousands. VEEV infection causes up to 35% mortality in children, 75% of which involve CNS penetration, causing severe long-term neurological disorders. VEEV is not only a naturally emerging disease threat but is also a highly developed biological weapon amenable to warfare or terrorism due to its aerosol transmission route and associated lethal meningoencephalitis. IFN signaling pathways and $\alpha\beta$ and $\gamma\delta$ T cell response from innate and adaptive immunity can control VEEV targeting of CNS, where virus-specific antibody responses are critical in limiting viral spread. In the absence of antibodies, VEEV replicon particles can induce T cell responses able to induce recovery from VEEV-induced encephalomyelitis, where cytotoxic $CD4^+$ T cells control VEEV in CNS lesions. VEEV vaccines induce robust neutralizing antibodies for protection against rechallenge. TC-83 vaccine responders have circulating PBMC biomarkers, and military programs give boosters of C-84 to those failing to seroconvert.

In contrast to these other viruses, RABV replication only begins after CNS penetration, as facilitated by depth of bite by its canine vector, thereby limiting possible detection of primary viral antigen in the periphery and resulting in delayed and minimal innate and humoral responses. Once RABV-related acute encephalitis symptoms begin, fatality is sure to follow due to absence of CNS infiltration by adaptive immune effector cells as a result of virus-induced decreases in BBB permeability. Other countermeasures against protection are tight MHC expression regulation and apoptotic phenotypes of BBB-infiltrated T cells. RABV vaccines cause increases in Ig, but little is known concerning vaccine-associated adaptive immune responses.

7. HEMORRHAGIC FEVER VIRAL DISORDERS

Viral hemorrhagic fever (VHF) classification originates from the study of hantaviral hemorrhagic fever (HF) and was later extended to include Crimean–Congo HF and Omsk HF. VHF can results from infection by 23 enveloped RNA viruses from four families: *Flaviviridae, Filoviridae,*

Arenaviridae, and Bunyaviridae. VHF designation is given to severe febrile illnesses with abnormal vascular regulation and vascular damage (Peters and Zaki, 2002). Vascular dysregulation occurs early in the course of disease, visible as skin flushing, hypotension, and conjunctival vasodilation, whereby vascular damage with capillary leakage occurs as disease progresses, causing edema and serous effusions of pleural and peritoneal cavities. The terminal phase of VHF, or shock, arises from increased disease severity from combinations of vascular dysregulation and damage from capillary leakage (Paessler and Walker, 2013). Detailed mechanisms of hemorrhage and plasma leakage during VHF include endothelial injury, activation of the mononuclear phagocytic system, cytokine storm, platelet aggregation and consumption, activation of the coagulation cascade, and insufficiency of coagulation factors from severe hepatic damage (Schnittler and Feldmann, 2003; Chen and Cosgriff, 2000). These mechanisms vary among diseases, cell and organ tropism of causative viruses, and host responses (Paessler and Walker, 2013).

Flaviviruses, filoviruses, arenaviruses, and bunyaviruses are the main causes of HF (Table 1). These viruses continue to propagate as part of the life cycles of primates, bats, rodents, farm animals, mosquitoes, and ticks. Infection by these viruses can cause mild vascular instability to fatal shock, with hemorrhage ranging from unnoticeable to life-threatening. Pathogenic mechanisms of HFV are diverse and include hepatic necrosis leading to deregulation of coagulation factors, cytokine storm, increased permeability, and complement activation. Overall disease severity by these viruses is varied, whereby ebola and Marburg HF can cause high fatality rates, whereas YF and dengue infections can be asymptomatic. Severe VHF is commonly correlated with ineffective immunity and high viral loads, and severe plasma leakage can occur from viral clearance and fever breaks in dengue HF (DHF).

7.1 Flavivirus Classification, Epidemiology, Immunology, and Vaccinology

Approximately 73 viruses are included in the *Flavivirus* genus of the *Flaviviridae* family of viruses, with 40 of these species associated with dengue, YF, JE, tick-borne encephalitis, and West Nile encephalitis as the most important arboviruses causing extensive global morbidity and mortality (Diamond, 2003). Flaviviruses are enveloped viruses with single-stranded RNA genomes that are translated in the cytoplasm to generate a single polyprotein that is then cleaved into structural and NS proteins by virus and host proteases. The various encoded viral proteins include capsid, envelope for

receptor binding, membrane fusion and viral assembly, and transmembrane proteins (prM) that assist in protein folding and function.

Although the precise mechanism is unclear, flaviviruses are believed to evade the immune system to enter the brain and spinal cord via circulating blood (Johnson and Mims, 1968), where these may cross the BBB by passive transport across the endothelium, by active replication in endothelial cells, or by a "Trojan horse" mechanism utilizing inflammatory cells (Solomon and Vaughn, 2002). IFN-dependent and complement system innate immune responses and humoral immunity, producing neutralizing antibodies limit dissemination of infection and protect against viral spread, reviewed in Diamond (2003). Cellular immunity is also important toward eradication of infected cells, whereby infection induces the recognition of flavivirus-infected cells by virus-specific CTLs, which then become activated, proliferate, and release inflammatory cytokines (Kesson et al., 1987; Kurane et al., 1989a; Liu et al., 1989; Murali-Krishna et al., 1996). However, there is also evidence that flavivirus replication is enhanced by myeloid cells and has been observed for dengue, YF, West Nile, tick-borne, and JE viruses (Diamond, 2003).

YF virus (YFV) is important both historically and currently. It was once one of the most globally feared diseases terrorizing Africa, Europe, and the Americas. Hundreds of thousands were killed in the Americas over a 250-year span—crippling economies (Watson and Klimstra, 2017). YFV is a member of the genus *Flavivirus* of the *Flaviviridae* family and contains a single-stranded RNA genome of approximately 11 kb. YFV virions are icosahedral and are composed of nucleocapsid, composed of capsid (C) protein subunits and a surrounding lipid bilayer derived from host membranes. The viral envelope is studded with dimers of envelope (E) and membrane (M) proteins, for a total diameter of approximately 45 nm. As the major component of the virion surface, the E protein is responsible for cell-surface receptor binding, virion assembly, fusion, and immunogenicity. Viral proteins are encoded in a single open reading frame and produced as a polyprotein later processed by proteolytic cleavage into structural (C, M, and E) and NS proteins (NS1, NS2a, Ns2b, Ns3, NS4a, Ns4B, and NS5), reviewed in Gardner and Ryman (2010).

During most YFV infections, the virus is transmitted by the bite of an infected *Aedes aegypti* mosquito found in urban areas. Infected patients often develop severe acute illness hemorrhagic YF disease, with associated symptoms of fever, nausea, vomiting, epigastric pain, hepatitis, jaundice, renal failure, hemorrhage, and shock, with 20%–60% of cases resulting in death

(Watson and Klimstra, 2017). YF is the prototypical VHF, sharing many pathophysiological features with other viral disorders only associated via similarities in syndromes, but with the exception that YF causes the most severe symptoms of hepatic dysfunction (Monath and Vasconcelos, 2015). YFV remains endemic in South American and African countries, with monkeys as its reservoir, causing regular outbreaks of jungle YF, and resulting in as many as 200,000 infections per year causing 30,000 deaths. Millions are at risk for infection in Africa, where vaccination prevalence is low. The 2016 outbreak in Angola serves as an example of YFV traveler-associated spreading to neighboring countries, where it reached as far as China, then naïve for virus (Watson and Klimstra, 2017), and representing a prime population for a major outbreak of epic proportions (Wasserman et al., 2016). Geographical shifting of mosquito populations to North America is also creating new risk for YFV, dengue, and Zika infection of naïve populations (Monaghan et al., 2016). Despite the availability of vaccination against YFV since the 1940s, large epidemics have still arisen, with dramatic surges of YFV in Africa in the 1960s and the late 1980s, with each reporting over 100,000 cases. Recent outbreaks have also affected Brazil, Paraguay and Argentina, Uganda, and Sudan and Ethiopia. Immunity is the critical for reducing and eliminating viral infections, but other contributing factors to virus amplification are multifactorial and elusive, including the emergence of new viral strains and prolonged periods of hot and humid weather promoting insect propagation, reviewed in Monath and Vasconcelos (2015).

Fifty-seven million people were vaccinated against YF across Africa between 2007 and 2010. Five hundred million doses of the live-attenuated YF 17D vaccine, representing the most effective vaccine ever created, have been distributed over the last 50 years (Monath and Vasconcelos, 2015). Both humoral and cellular immunity elicited by 17D are observed and well characterized, where neutralizing antibodies provide protection, but 17D also provides a robust, long-lived, and polyfunctional adaptive T cell immune response (Watson and Klimstra, 2017). Neutralizing antibodies remain the accepted correlate of protection against YFV, with 90% or greater of 17D immunized individuals developing neutralizing antibodies (Gotuzzo et al., 2013). 17D also elicits a complex modulation of innate immune cytokines, with elevated levels of plasma IFN-γ 15 days postvaccination (Neves et al., 2009). Restimulation of innate immune cell cultures of NK cells, neutrophils, and monocytes from 17D vaccinated humans with YF antigen results in the increased production of IFN-γ, IL-1beta, IL-10, IL-12, TNF-α, and IL-10 (Neves et al., 2009; Gardner and Ryman, 2010;

Luiza-Silva et al., 2011; Silva et al., 2011). Since its development, humoral immunity, as a gold standard of general vaccine development, was the most studied aspect of human immunity to 17D. However, recent studies of adaptive T cell—mediated immunity to 17D have demonstrated that both $CD4^+$ and $CD8^+$ T cells strongly respond to 17D, with activated $CD8^+$ T cells detected as 3 days after vaccination (Akondy et al., 2015), and $CD4^+$ T cells detected several days later (Akondy et al., 2015; Kohler et al., 2012; Blom et al., 2013). Increased $CD8^+$ T cell proliferation correlates directly with the levels of virus genomes in plasma, which peaks once virus is eliminated (Akondy et al., 2015). $CD8^+$ T cell clones responding to 17D differentiate into central memory and effector memory subpopulations (Dewitt et al., 2015) and are still detectable 25 years following vaccination (Wieten et al., 2016). 17D-specific $CD8^+$ T cells respond to epitopes contained from every protein product generated by the 17D polyprotein, and upon peptide restimulation, these 17D-specific $CD8^+$ T cells have activated cytotoxic profiles including increased expression of IFN-γ, TNF-α, and MIP1-β and IL-2 granzyme B and CD107a (Blom et al., 2013; Akondy et al., 2009) but are not exhausted and retain long-lived memory and polyfunctional phenotypes for at least 2 years following 17D rechallenge (Akondy et al., 2009).

Dengue virus (DENV), also a member of the single-stranded positive-sense RNA viruses from the *Flaviviridae* family, causes visceral and CNS disease in humans and is closely related to YFV, where DENV fever has often been mistaken for YFV infection. Far more serious is DHF, where additional symptoms develop, including hemorrhage and shock, and have mortality rates exceeding 30% if left untreated (Rogers et al., 2006). DENV is a spherical, 50-nm virion, comprising of three structural proteins: capsid (C), premembrane and membrane (prM and M), and envelope (E). The E protein directs several critical steps of the viral replication cycle, including engagement with cellular attachment and entry factors, membrane fusion, and virion assembly. DENV binds to target cells via glycosaminoglycans, C-type lectins such as DC-SIGN, the mannose receptor CD206, and immunomodulatory proteins (TIM and TAM receptors; Diamond and Pierson, 2015). Thus targets for DENV infection include monocytes, macrophages, DCs, mast cells, and possibly hepatocytes and endothelial cells. Following its entry into the cellular cytoplasm, the viral genomic 10.7 kb RNA is translated into a single polyprotein, later cleaved into three structural and seven NS proteins (NS1, NS2a, Ns2b, Ns3, NS4a, Ns4B, and NS5) by viral NS3 and host cell proteases. Twenty-five percent of DENV infections cause both mild symptoms including dengue fever (DF) to

more severe and lethal DHF, causing shock via hemorrhagic and capillary leak syndrome. DF can be characterized by abrupt onset febrile illness causing headache, severe muscle and joint pain, and rash, whereas DHF is characterized by rapid onset capillary leakage accompanied by significant thrombocytopenia and liver injury (Halstead, 2007).

As with YF, DENV origins are believed to be that of a sylvatic virus, with a natural life cycle involving multiple mosquito and vertebrate species from Asia and Africa (Diallo et al., 2003). DENV adaptation to human demography is via mosquito vector *Aedes aegypti*, breeding in urban areas (Trpis and Hausermann, 1986). Cases of DENV infection have increased since the 1960s, with an estimated 50 million cases of DF, and 500,000 cases of DHF occurring globally every year. There are no cures for DENV-associated disorders, and vaccine development has been complicated by antibody-dependent enhancement of future heterotypic infection induced by vaccination (Vaughn, 2000; Halstead and Deen, 2002). Thus avoidance and control of *Aedes aegypti* is the best approach for limiting DENV infection (Rogers et al., 2006).

Adaptive immune $CD8^+$ T cells vigorously and frequently recognize DENV NS3, NS4B, and NS5 proteins, whereas the capsid, envelope, and NS3 proteins are the dominant targets for $CD4^+$ T cells (Simmons et al., 2005; Duangchinda et al., 2010; Weiskopf et al., 2011, 2013; Rivino et al., 2013). Both $CD4^+$ and $CD8^+$ T cells are believed to contribute to protection against DENV, as DENV-specific $CD4^+$ T and $CD8^+$ T cells proliferate, produce IFN-γ, and lyse target cells, from primary DENV infection (Kurane et al., 1989b; Mathew et al., 1996; Gagnon et al., 1999; Livingston et al., 1995). Higher frequencies of DENV-specific IFN-γ-producing T cells are present in children with asymptomatic DENV infection (Hatch et al., 2011). Both $CD4^+$ and $CD8^+$ T cells contribute to protection against DENV challenge (Yauch et al., 2009, 2010; Zompi et al., 2012; Zellweger et al., 2013), and HLA alleles associated with increased risk of DENV severity correlated with weak $CD8^+$ T cell responses and vice versa, implying a protective role for $CD8^+$ T cells against severe DENV disease in humans (Weiskopf et al., 2013).

In 2015, the first dengue vaccine (Dengvaxia) was licensed in Asian and South American countries for protection against all four DENV serotypes, and while it demonstrated an good safety and efficacy in clinical trials, it has recently been withdrawn in the Philippines due to its causing elevated disease severity if administered following infection (Wichmann et al., 2017). It has been suggested that failure of this and other live-attenuated

tetravalent dengue–YF chimeric virus vaccines (Guy et al., 2011) is the result of their lacking the NS proteins NS3, NS4B, and NS5, otherwise dominantly targeted by $CD8^+$ T cells (Simmons et al., 2005; Duangchinda et al., 2010; Weiskopf et al., 2011, 2013; Rivino et al., 2013), making it critical to accurately assess not only antibody responses but rather T cell responses in the context of DENV vaccine development (Weiskopf and Sette, 2014).

7.2 Mammarenavirus Classification, Epidemiology, Immunology, and Vaccinology

Lassa virus (LASV), causing Lassa fever (LF), is an enveloped virus with two single-stranded RNA segments and is another virus causing HF. LASV is an Old World member of the *Arenavirida* family of viruses. The single-stranded arenavirus genome consists of a small (S) and a large (L) RNA segment, measuring 3.4 and 7 kb, respectively. The large segment encodes a small zinc-binding (Z) protein which regulates transcription, replication, and viral budding, along with the RNA polymerase (L). The small segment encodes the NP and the two envelope glycoproteins (GP1 and GP2) responsible for cell entry, reviewed in Russier et al. (2012).

LASV disorder is endemic in Africa and its neighboring countries (Safronetz et al., 2010; Gunther et al., 2000), and though infection rates are difficult to quantify due to limited survey infrastructure, classification of its clinical symptoms is common to other diseases. LASV is predicted to be responsible for approximately 300,000 infections and up to 6000 resultant deaths each year (Ogbu et al., 2007; Mccormick et al., 1987). Transmission to humans is via the rodent host *Mastomys natalensis* (Mccormick et al., 1987). APCs, DCs, and macrophages are believed to be the first cells targeted by LASV infection (Baize et al., 2004; Mahanty et al., 2003), which can rapidly speed up dissemination of LASV to multisystem organs due to their widespread physiological distributions in mucosal tissues and skin. Due to their ease in motility across various organs and tissues, APCs are believed to the responsible for the spread of LASV for the establishment of systemic infection (Hensley et al., 2011). APC infection results in substantial virus release in the secondary lymphoid organs, the liver, hepatocytes, fibroblasts, and endothelial cells that are subsequently infected. Lymphopenia of $CD4^+$ and $CD8^+$ T cells, NK cells, and B cells is observed early during disease onset, reviewed in Russier et al. (2012).

LASV infection severities range from asymptomatic infection to fatal HF (Fisher-Hoch et al., 1995) and commonly resulting from other viral infections, nonspecific symptoms beginning several days after infection include fever, headache, arthralgia, myalgia, and severe asthenia. These early symptoms are typically followed by more severe symptoms of pharyngitis, conjunctivitis, cough, abdominal pain, diarrhea, and vomiting. In severely affected patients, cervical and facial edema, hemorrhages, renal and liver failures, and encephalopathy occur, and death follows systemic shock (Edington and White, 1972). Survivors of LASV-related disorders have persisting lifelong morbidities and disabling conditions including deafness (Cummins et al., 1990). No vaccine has been licensed against LASV, and ribavirin is the only existing treatment, but is only effective if administered very early after infection and is not available for broad distribution in countries where LASV is endemic (Mccormick et al., 1986).

T cells play a crucial role in the outcome of severe LASV infection, which has been associated with defective T cell responses since the very cells responsible for stimulating T cell antigen responses are those infected by the virus. However, T cell responses have been demonstrated to play critical roles in the control of LASV, where strong memory $CD4^+$ T cell responses directed against LASV NP and GP proteins are observed in LASV-seropositive healthy individuals from endemic regions (Ter Meulen et al., 2000; Meulen et al., 2004). High serum concentrations of IL-8 and CXCL10 chemokines that attract and activate T cells are associated with nonfatal LASV infections (Christensen et al., 2006; Dufour et al., 2002) and vice versa in fatality cases (Mahanty et al., 2001). The control of acute LF has been correlated with increases in circulating activated $CD4^+$ and $CD8^+$ T cells in response to LASV infection or antigen (Baize et al., 2009). In vaccine studies, protection against a lethal LASV rechallenge is associated with the induction of T cell immunity (Fisher-Hoch et al., 2000; Geisbert et al., 2005). However, in comparison to other viruses, LASV-infected DCs are unable to mount effector T cell responses (Pannetier et al., 2011). Human and nonhuman primate studies have demonstrated that LASV NP and GP proteins are the main viral antigens recognized by activated T cells (Meulen et al., 2004; Ter Meulen et al., 2000; Fisher-Hoch et al., 2000; Fisher-Hoch and Mccormick, 2001, 2004; Geisbert et al., 2005), suggesting that vaccines using these proteins to induce long-term memory T cell expansion will best control the spread of LF.

7.3 Filoviruses Classification, Epidemiology, Immunology, and Vaccinology

Ebola virus (EBOV) causes a rapidly fatal HF for which there is currently no treatment (Muyembe-Tamfum et al., 2012; Team et al., 2014). EBOV is a member of the *Filoviridae* family, which are filamentous, negative-stranded RNA viruses that cause severe human disease. Filoviruses viruses are variable, with long filaments measuring 80 nm in diameter and which can reach lengths of up to 1000 nm, with many turns and branches and which have tendency to curve to resemble the number 6. Viruses are composed of nucleocapsid, matrix, and envelope proteins, whereby seven genes encode NP, the viral proteins VP24-VP30-VP35-VP40, L (polymerase), and the GP (Hoenen et al., 2006), expressed as GP1 and GP2, and regulating virus production and release (Mohan et al., 2015). NPs embed the genome in complex with VP30 and VP35 for RNA synthesis. VP40 and VP24 proteins are localized in virus matrix space (Watanabe et al., 2007; Hoenen et al., 2010). EBOV is transmitted to humans via mucosal surfaces, skin injury, and vertical transmission (Feldmann and Geisbert, 2011), and with the exception of T cells, can infect almost all human cells using various different attachment mechanisms, reviewed in Falasca et al. (2015). Both innate and adaptive immune responses are involved in EBOV pathogenesis, where innate immune deregulation involves inhibition of type-I IFN response and perturbation of cytokine signaling, along with impairment of DC and NK cells, and adaptive immune deregulation involves both humoral and cell-mediated immunity (Falasca et al., 2015).

Because high levels of EBOV replication are associated to multiple cell types, its associated systemic dissemination results in a highly complex pathogenesis model, including detrimental immune suppression and hyperactivation, and leading to disordered coagulation and tissue damage, that, in the absence of treatment, results in rapid multiple organ failure and death within days of symptomatic infection (Baseler et al., 2017). For 50 years, EBOV and related filoviruses have been repeatedly re-emerging to cause large epidemics of highly fatal HF. Ongoing EBOV outbreaks in Africa has brought this virus to the forefront of research, with over 20,000 reported cases of infection and an associated 8000 deaths (Mcelroy et al., 2015).

Natural serologic response to EBOV infection involves virus-specific IgM and IgG antibody responses sometimes detected early, but usually later, once symptoms begin (Ksiazek et al., 1999; Rowe et al., 1999). EBOV-infected DCs are impaired in cytokine production required for T cell

activation (Mahanty et al., 2003), whereas infected macrophages are unable to mature (Bosio et al., 2003). EBOV is classified as an immunosuppressive virus since numerous of its proteins interfere with immune responses by inducing T cell apoptosis, lymphopenia, and absence of antibody responses in fatal cases (Basler and Amarasinghe, 2009). Classification of EBOV-targeting mechanisms has been compromised by lack of infrastructure for adequate biosafety containment level facilities required to analyze this deadly virus. However, observations of the adaptive T cell immune response have shown that EBOV correlates with fatal outcomes by causing aberrant cytokine responses (Baize et al., 1999, 2002; Wauquier et al., 2010; Villinger et al., 1999; Ansari, 2014), decreased $CD4^+$ and $CD8^+$ T cells, and increased apoptotic T cell phenotypes (Baize et al., 1999; Wauquier et al., 2010; Geisbert et al., 2000; Bradfute et al., 2010; Gupta et al., 2007). In recent work, EBOV induced increased $CD4^+$ and $CD8^+$ T cell activation against the viral NP, with $CD8^+$ T cells demonstrating the largest increases in expression of activation and proliferation biomarkers, with sustained activation following EBOV clearance and following patient discharge, suggesting continued antigen stimulation after resolution of the disease (Mcelroy et al., 2015). Recently, an rVSV-ZEBOV recombinant, replication—competent vesicular stomatitis virus—based vaccine expressing a surface GP of Zaire ebolavirus, demonstrate a 100% efficacy in preventing EBOV disease in contacts and contacts of contacts of recently confirmed cases in Guinea, West Africa (Henao-Restrepo, 2017 #550). This vaccine produced rapid innate immune responses after a single dose, suggested to lead to longer-term full protection by providing an essential period of restricted virus replication during the development of specific adaptive responses (Marzi, 2015 #551).

7.4 Orthonairovirus Classification, Epidemiology, Immunology, and Vaccinology

Crimean-Congo hemorrhagic fever virus (CCHFV) is a tick-borne virus causing HF resulting in human fatalities. CCHFV is a member of the *Nairoviridae* family of viruses from the genus of *Orthonairovirus* and the order of the Bunyaviridae viruses. It has a single-stranded, negative-sense RNA genome possessing three segments: the large (L), medium (M), and small (S) segments (Casals, 1969; Clerx et al., 1981). The L segment encodes the viral RNA-dependent RNA polymerase responsible for mRNA synthesis and RNA replication (Honig et al., 2004). The M-segment encodes numerous NS and two structural GPs (GN and GC) responsible

for cell tropism and attachment and are targets for neutralizing antibodies. The S-segment encodes the viral NP binding the RNA segments toward formation of ribonucleoprotein complexes (Altamura et al., 2007; Sanchez et al., 2006).

Though HF by CCHFV infection in humans is not among the most common viral disorders reported, it remains important because it is fatal in up to 30% of cases (Bente et al., 2013; Goedhals et al., 2017). Transmission of CCHFV to humans occurs through contact with infected animal blood, or ticks, belonging to the genus *Hyalomma*, as its primary vectors and providing transit from one infected human to another (Mousavi-Jazi et al., 2012). CCHFV human infection involves sudden onset of acute symptoms, including high fever, headache, myalgia, and petechial rash, followed by hemorrhage progressing to multiorgan failure, with leukopenia, thrombocytopenia, and elevated liver enzymes as hallmarks of the overall disorder (Begum et al., 1970; Sanchez et al., 2006). Outbreak-associated fatality rates are varied but can reach 70% (Mousavi-Jazi et al., 2012). There is currently no licensed vaccine, and use of Ribavirin as treatment has been investigated but remains controversial (Begum et al., 1970; Bente et al., 2010). Distribution of CCHFV infection and associated disease follows geographical spread of the principal vectors (Bente et al., 2013; Whitehouse, 2004). Clinical CCHFV disorders are described in Africa, Asia, the Middle and East Eastern Europe, and have recently emerged in other countries including Turkey, India, Spain, and Greece, and with almost 10,000 cases reported in Turkey between 2002 and 2015 (Maltezou et al., 2010; Papa et al., 2008; Leblebicioglu et al., 2016).

Typically, transient IgM and IgG antibody responses develop within days following primary CCHFV infection and can persist long-term (Shepherd et al., 1989; Burt et al., 2013), but where lack thereof usually results in fatality (Shepherd et al., 1989). IgM and IgG antibodies have however not been correlated with clearance, viral load, or outcomes (Duh et al., 2007), implying that innate and T cell immunity must be critical for viral clearance. Neutralizing antibodies also do not cause protection, and non-neutralizing antibodies may assist in antibody-dependent cell-mediated cytotoxicity (Bertolotti-Ciarlet et al., 2005). Thus, as immune correlates of protection for CCHFV are not well documented, vaccine design has aimed at targeting the CCHFV NP or GPs. Only an inactivated vaccine is available, and even though the attaining of immunogenicity has required its administration in multiple doses, it was demonstrated to reduce infections and induce both neutralizing antibody responses and T cell responses to NP

peptides (Mousavi-Jazi et al., 2012). Another promising approach is the use of modified VACV Ankara recombinant vaccine expressing the viral GPs, which induce cellular and humoral responses and which are observed to provide protection from lethal disease in mice (Buttigieg et al., 2014; Dowall et al., 2016). Although T cell responses are known to play a role in protection from and clearance of viral infections, it was only recently that specific $CD8^+$ T cell epitopes against GN and GC were shown to stimulate IFN-γ production, whereby responses were detectable several years after the acute CCHFV infection, even in the absence of continued antigenic stimulation, and where IFN-γ-producing $CD8^+$ T cells were confirmed as responsible for providing long-term protection (Goedhals et al., 2017).

7.5 Hemorrhagic Fever Viral Disorders and Adaptive Immune Responses Summary

VHFs causes high fatality rates and are commonly correlated with ineffective immunity and high viral loads. YFV is important for both historical and current reasons. Historically, it crippled economies and families by killing hundreds of thousands over 250 years. YFV is transmitted by mosquitos in urban areas, causing as many as 200,000 infections and 30,000 deaths annually. Like other mosquito vector viruses, YFV is an existing and re-emerging threat due to increased geological spread by both world travelers and shifting mosquito breeding geographies. Flaviviruses evade immunity to enter the brain and spinal cord via circulating blood, crossing the BBB via "Trojan horse" mechanism. Dissemination of infection and protection against YFV is elicited by IFN-signaling, complement system, and other innate, humoral, and adaptive immune responses. Neutralizing antibodies are still the gold standard correlates of protection, but evidence that a robust, long-lived, and polyfunctional adaptive $CD4^+$ and $CD8^+$ T cell immune response is what is provided, early after vaccination by the 500 million doses of effective YF 17D vaccine distributed globally. Importantly, these are nonexhausted, polyfunctional central memory and effector memory T cell subsets that are detected for over 25 years following vaccination.

Far more serious is DHF by infection by DENV, contributing to either mild or severe HF, with mortality rates exceeding 30% in the untreated. As with YFV, DENV uses mosquitos adapted to urban areas as their vectors. Fifty million cases of DF and 500,000 cases of DHF occur globally each year, with no available cures for its associated disorders and where vaccine development has been complicated by antibody-dependent vaccine-induced enhancement of future heterotypic infections. Cytotoxic $CD8^+$

and $CD4^+$ T cells, however, vigorously and frequently recognize DENV proteins and are believed to contribute protection against primary infection. The DENV vaccine Dengvaxia has been recently withdrawn, with its failure posited to result from its lack of DENV proteins specifically targeted by $CD8^+$ T cells, and demonstrates that is essential to accurately assess T cell responses in the context of DENV development.

LASV also causes mild and severe VHF and may cause 300,000 infections and up to 6000 deaths each year. LASV is transmitted to humans by a rodent vector and first targets Apc, Dc, and macrophages, contributing to rapid multisystem and organ LASV dissemination due to their widespread physiological distributions. LASV also causes lymphopenia of $CD4^+$ and $CD8^+$ T cells, NK cells, and B cells, and survivors of LASV-related disorders can be expected to maintain lifelong morbidities. There is no licensed LASV vaccine as of yet, complicated by the fact that the very cells responsible for stimulating T cell antigen responses are those infected by the virus. However, control of acute LF is correlated with increased circulating strong memory $CD4^+$ and $CD8^+$ T cells in response to LASV infection or rechallenge and LASV antigen.

EBOV also causes mass HF. It can infect almost all human cells with exception of lymphocytes and has no known treatment despite documented involvement of innate and adaptive immune responses. Classification of EBOV targeting mechanisms are compromised by lack of infrastructure for adequate biosafety containment level facilities. EBOV causes DCs to be impaired in cytokine production for T cells activation and inhibits macrophages maturation, thus classifying it as an immunosuppressive virus, with fatalities correlating with its induction of lymphopenia the absence of antibody responses. EBOV, however, causes increased $CD4^+$ and $CD8^+$ T cell activation, with recorded persistence of activated $CD8^+$ T cells in survivors. The knowledge that $CD4^+$ and $CD8^+$ T cell responses are against the EBOV NP will be useful for the design of efficient targeting vaccines.

CCHFV also causes HF yielding fatalities in up to 30% of cases. There is no current vaccine, and CCHFV has recently reemerged in naïve countries in response to geographical relocation of its primary tick vector. Infection by CCHFV causes transient Ig antibody responses, inversely correlating with sure fatality, but not correlating with clearance, viral load, or outcomes. No protection is granted by neutralizing antibodies either, implying that innate and T cell arms of immunity are critical for viral clearance. With little to no immune correlates of protection for CCHFV, vaccine design has aimed at targeting the CCHFV NP or GPs, where immunogenicity requires

the administration of multiple doses to induce both neutralizing antibody responses and T cell responses. Only recently, specific $CD8^+$ T cell epitopes against these CCHFV proteins have been confirmed to stimulate cytotoxic $CD8^+$ T cells providing protection in survivors.

8. PERSPECTIVES

Despite many documented instances of virus eradication from populations by earlier vaccination strategies, there is a continuous imminent risk of outbreaks of pandemic proportions by existing and emerging viruses, as a result of anti-vaccination campaigns, unforeseen viral strain recombination, exposure of naïve populations to viruses by infected world travellers, a rapidly growing and aging and immunocompromised world population, acts of bioterrorism, and use of viruses as biological weapons in war. Past strategies in the development of certain vaccines have often been lucky in their efficacies due to their eliciting both humoral and long-lasting adaptive T cell immunity, whereas others have failed and have only induced shorter lived humoral responses that do not always confer long-lasting protection. The precise and likely overlapping mechanisms dictating lifelong immunity conferred by successful vaccines against smallpox, measles, mumps, rubella, polio, and YF are not completely understood. What has become clear however is that innate immunity usually primes adaptive immunity to confer this long-term protection. It is not a lack of existing immune-monitoring methodologies but rather perhaps a lack of their correct implementation in the continued analysis of vaccinated individuals that are hampering the gaining of this important knowledge. Therefore it seems there is an urgent need for the standardization of vaccine methodologies adequately measuring effector memory T cell responses and host-immune evasion mechanisms in appropriate animal models and humans and through the use of multiparametric immune-monitoring platforms able to simultaneously document numerous immune cell phenotypes across time postexposure, vaccination, or rechallenge. The importance of global development of standardized procedures of biospecimen banking from vaccinated individuals cannot be understated and will provide unprecedented statistical power in the analysis of the balance between the innate and adaptive immune arms conferring lifelong resistance to infection. The standardization of these methodologies should better assist future rational design of vaccines and boost confidence toward the mass production and stockpiling of these critical prophylactic measures against otherwise crippling and lethal viral disorders.

ACKNOWLEDGMENTS

This work was supported by grants from the Canadian Foundation for HIV-1/AIDS Research (CANFAR) and the Canadian Institutes of Health Research (CIHR). The authors wish to acknowledge Laura D Kramer, PhD, Arbovirus Laboratory, Wadsworth Center, New York State Department of Health, and School of Public Health, State University of New York at Albany, for her contributions to Table 1.

CONTRIBUTIONS

A.M. drafted the manuscript and both authors edited and revised the final version.

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