

COVID 19 Vaccines: Should we fear ADE?

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Conflicts: The authors have no conflicts to reveal.

Summary: Coronavirus vaccines have sensitized animals to enhanced disease during live virus challenge. Predominant infection of parenchymal not myeloid cells lessens risk of intrinsic vaccine antibody dependent enhanced disease (iADE). Rubella or measles inactivated vaccine like hypersensitivity (VAH) reactions threaten.

Abstract: Might COVID 19 vaccines sensitize humans to antibody dependent enhanced (ADE) breakthrough infections? This outcome is unlikely because coronavirus diseases in

humans lack the clinical, epidemiological, biological or pathological attributes of ADE disease exemplified by the dengue viruses (DENV). In contrast to DENV, SARS and MERS CoVs predominantly infect respiratory epithelium, not macrophages. Severe disease centers on older persons with pre-existing conditions and not young infants or individuals with previous coronavirus infections. Live virus challenge of animals given SARS or MERS vaccines has resulted in vaccine hypersensitivity reactions (VAH), similar to those in humans given inactivated measles or respiratory syncytial virus vaccines. Safe and effective COVID 19 vaccines must avoid VAH.

KEY WORDS: dengue, dengue hemorrhagic fever, antibody dependent enhancement (ADE), vaccine adverse events, coronavirus, SARS CoV-1, SARS CoV-2, immunopathology, vaccine, hypersensitivity, antibody, T cells.

Introduction. Not since pandemic smallpox or the 1918 influenza have humans confronted a epidemic viral pathogen as successful as SARS CoV-2, a member of a family of viruses that cause serious diseases in many vertebrates.[1] It has proved difficult to achieve robust vaccine protection against avian, bovine, porcine, canine and feline coronaviruses, failures sometimes attributed to “antibody dependent enhancement (ADE).” [2] The possibility that a SARS CoV-2 vaccine may sensitize recipients to ADE has received considerable scrutiny.[3] On inspection, ADE is not one but two vaccine-related immunopathological phenomena: intrinsic ADE (iADE) and vaccine hypersensitivity (VAH). iADE describes interactions between IgG antibody and microbial pathogen immune complexes that attach to Fc receptors to initiate infection but also enhance replication of the microbe by suppressing innate cellular immune defenses.[4, 5] VAH was first described in humans in the early 1960s, after formalin-inactivated measles vaccines were introduced in the US and Europe. Within months large numbers of vaccinated children developed a severe breakthrough disease, called “atypical measles.” [6] A similar outcome, “vaccine associated enhanced respiratory disease (VAERD),” was observed in infants, 4 – 12 months of age, who were given formalin-inactivated respiratory syncytial virus (RSV) and a few months later infected by RSV.[7] The outcomes observed were attributed to delayed type hypersensitivity and/or an Arthus reaction.[8] Lung lesions revealed damage to parenchymal tissue, a pulmonary neutrophilia with abundant macrophages and lymphocytes and excess eosinophils. From studies in laboratory animals, it is thought that formalin de-conformed viral antigens raised non-protective antibodies that led to a Th2 polarization of the immune response and a deficit of cytotoxic T cells. It was also the case that mice immunized with RSV inactivated with UV radiation, a purified fusion (F) protein, or a vaccinia-RSV replicative construct experienced similar pathology following challenge with wild-type virus. A similar pathological response has repeatedly accompanied live virus challenge in several species of laboratory animals

vaccinated with SARS and MERS CoV constructs, with and without adjuvants.[9, 10] VAH may best be defined as a Coombs type III antigen hypersensitivity. It should be emphasized there is no formal proof that VAERD is antibody mediated. The mechanism(s) of the post-measles vaccine disease enhancement and its similarity to VAERD are not known.

The biological behavior of some coronaviruses in non-human species together with evidence that human coronavirus antibodies enhanced infection of SARS or MERS CoVs in Fc receptor-bearing cells, *in vitro*, have led to speculations that ADE contributes to disease severity in humans.[11] It has been reported that high levels of SARS CoV-1 IgG antibodies circulated in severe SARS cases and that anti-S IgG neutralizing antibody (NAb) responses developed significantly faster after the onset of clinical symptoms in fatal compared with recovered cases leading some to attribute enhanced tissue damage to ADE. [12] Because sera from SARS or MERS vaccinated animals sera enhanced CoV infections, *in vitro*, it was assumed that post-vaccination pathologies, too, were ADE responses. [13]

DENGUE ADE If SARS or MERS infection outcomes are affected by iADE they should have epidemiological and disease features in common with DENV. These are compared in Table 1. *In vivo*, iADE requires an initial immunological event, termed “sensitization.” In dengue, this occurs in three settings: 1) first infections,[14] 2) multitypic dengue antibodies passively transferred to infants (high antibody levels protect, low levels enhance), [15] and 3) vaccination resulting in incomplete protective immunity.[16, 17] Crucial to the occurrence of iADE is the circulation of four antigenically related DENVs. After a first infection, there is a 1 – 2 year period of relative cross protection after which heterotypic DENV infection may cause severe disease. [18]Third or fourth sequential infections are not pathogenic. Pre-outbreak age-specific distributions of dengue antibodies control age-specific ADE disease attack rates. During heterotypic infections, viremias may be enhanced early but as illness progresses the titers and duration of viremias are shortened. [19]

Dengue disease is a serious and widespread global health problem. In many dengue endemic countries there is an estimated 2% lifetime risk of hospitalization for enhanced dengue disease.[20] Severe DENV iADE infections are short duration illnesses that elicit a stereotypical clinical course: an abrupt onset of fever and generalized symptoms followed around the time of defervescence by a rapid loss of fluid from the vascular compartment and, in turn, anoxia, shock and gastrointestinal hemorrhage. [21] The first suggestion of an immunopathology was finding that DENV infected peripheral blood leukocytes (PBL) from dengue-immune monkeys and humans but not PBLs from non-immune donors.[22] Severe DENV infections in infants implied that antibodies were etiological factors, a hypothesis confirmed when antibody mediated enhanced DENV infection was produced in monkeys. [23] Peak viremia titers observed early in illness are predictive of severe dengue in humans. [19] Careful pathologic studies identified splenic and lymph node monocytes, macrophages and dendritic cells as major targets of DENV infection. [24] Fluid loss from the vascular compartment is attributed to capillary damage caused by circulating toxic viral protein (nonstructural protein 1 - NS1).[25] In humans, disruption of endothelial glycocalyx components by NS1 correlates with plasma leakage during severe DENV infection.[26] DENV NS1-induced endothelial cell intrinsic pathway vascular leakage is related to loss of integrity of endothelial glycocalyx components both *in vitro* and *in vivo* and is independent of inflammatory cytokines.[27]

Two corollary iADE phenomena have been described: 1) passively acquired dengue antibodies efficiently enhance infection/disease and 2) disease severity rates may increase rapidly during epidemics. Severe dengue accompanies first infections in infants circulating dengue antibodies acquired from multi-immune mothers.[28] During the course of secondary DENV 2 epidemics in Cuba in 1981 and 1997, disease severity increased month to month. It has been suggested that a single amino acid mutation in non-structural protein 1 (NS1) may

have increased disease severity by enhancing viremia or improving efficiency of transmission of virus by vector mosquitoes. [29]

SARS ADE? A coronavirus disease of cats, feline infectious peritonitis (FIP), causes classic ADE disease.[30] The dominant *in vivo* target for FIPV infection is peritoneal macrophages. Passively acquired maternal antibodies convert FIPV infections in kittens from a mild disease to one with fatal outcome. Many FIP vaccine constructs have sensitized animals to breakthrough ADE infections. In contrast to FIP, SARS and MERS CoV infections in humans predominantly affect the respiratory tract and other organs but not the reticuloendothelial system. A prevailing hypothesis is that SARS CoV-1 and 2 enter cells via attachment of spike (S) protein to the ACE2 receptor. Most patients who die of SARS develop an acute respiratory distress syndrome. [31]Age based case fatality ratios for SARS and COVID 19 are similar. During 2001 – 3, among those infected with SARS CoV-1, fatalities occurred in less than 1% of those under 25 years-old, 6% among those ages 25 to 44, 15% in ages 45 to 64, and more than 50% in those 65 years or older. [31] SARS CoV-1 is a viral infection of alveolar epithelium resulting in diffuse alveolar damage, epithelial necrosis, fibrin and hyaline deposition accompanied by an infiltration of multinucleated giant cells with evidence of infection of macrophages in the alveoli and in lung interstitium. [32] The principal target of infection is alveolar epithelial cells, apparently directly damaged by virus.[32] Severe diarrhea is not matched with corresponding intestinal pathology and there is a discrepancy between the histological damage and widespread viral infection of liver, distal convoluted renal tubules, sweat glands, parathyroid, pituitary, pancreas, adrenal gland, skeletal muscle and cerebrum.[33] SARS CoV-1 infections are of long duration, characterized by virus shedding from the intestines, respiratory secretions and sweat exhibits an increase in infection intensity during the course of illness.[33] SARS CoV 1 infections usually result in a normal IgM to IgG transition, although IgG antibodies were sometimes

observed as early as 4 days after onset of illness. It is thought that competent T cell immunity is essential for recovery.[34]

While many clinical and pathological features are shared by SARS, MERS and COVID 19, lungs from patients with COVID-19 show distinctive severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis, microangiopathy and a reactive angiogenesis.[35] Indeed, there is growing evidence of thromboembolic phenomena in COVID 19.[36] In severe and fatal SARS and MERS the dominance of the inflammatory response gave rise to the concept that cellular damage was due to a “cytokine storm.”[37] Because cytokines are stimulated by viral infection itself, it is difficult to distinguish between cytokines as cause or effect of infection. “Cytokine storm” has also been invoked as a pathogenic mechanism in dengue, instead, capillary damage results from a circulating viral toxin. [25]

Concluding Remarks:

With others, we conclude that the differences in clinical, epidemiological and pathological features of SARS and DENV diseases suggest that iADE does not contribute to the severity of natural human coronavirus infections. [3] Because myeloid cells are not major targets of infection, vaccine derived non-protective coronavirus antibodies are not expected to produce iADE infections in humans. High case fatality rates in elderly persons with pre-existing conditions together with laboratory and autopsy studies support the contention that SARS CoV 1 and 2 are direct pathogens centering on type II pneumocytes, well-differentiated bronchial epithelial cells and other parenchymal cells.[38]. If SARS CoV 1 or 2 infection severity were modified by enhancing antibodies acquired earlier in life, severe and fatal cases should cluster in age groups reflecting the time of that past infection. A past infection age cluster effect is illustrated by the 2001 severe DENV 1 outbreak in Tahitian

children. [39]The island-wide DENV 1 and 3 infections that occurred in 1988-90 protectively immunized older children. However, children born after 1990 were sensitized by DENV 2 infections during 1966-67 explaining the occurrence of severe secondary DENV 1 disease in 4 – 12 year-olds in 2001.[39]

A question asked frequently is whether SARS or MERS CoV infections convey solid protective immunity. Viral respiratory infections often fail to protect the respiratory tract from reinfection by the same organism. Among immune individuals, respiratory tract superinfections occur frequently, but, usually without systemic disease. [40]For example, natural and vaccine immunes were re-infected with measles or rubella viruses and these infections may contribute to the spread of virus. [41]

VAH is a post-vaccination outcome that may be associated with non-protective antibodies. VAH is a complex and poorly defined immunopathology. Several different SARS and MERS vaccines have been shown to elicit a post-challenge VAH in laboratory animals. Ominously, when SARS-CoV-1-immune monkeys were challenged with homologous virus most animals had evidence of lung inflammation.[40] It is important to note that inactivated measles vaccine and Dengvaxia exhibited short-term protection.[6, 16] A central challenge to SARS CoV-2 vaccine development will be differentiating early from sustained protection and will be greatly aided by a SARS CoV-2 model of VAH in laboratory animal models. Recognition of vaccine constructs that achieve solid protection in humans might be accelerated by challenge of vaccinated human volunteers with live SARS CoV-2.[42] Better understanding of the clinical and immunological behavior of SARS-CoV-2 itself might be achieved through direct infections of human volunteers.[43] Given the magnitude of the repertoire of COVID 19 problems and the need for an effective vaccine, the full force of worldwide investigative resources should be directed at unraveling the pathogenesis of VAH.

Words: 1857

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Table 1. Dengue vs SARS CoV-1 & 2: Antibody Dependent Enhancement checklist

Risks	Dengue	SARS CoV-1 & 2
Sensitizing agent	4 dengue viruses	unknown
Host cell infected	Predominantly Monocytes, macrophages, mature dendritic cells[44]	Predominantly pulmonary epithelium[31]
Infected organs	Lymph nodes, spleen[24]	Lung; other organs
Sequence	2 nd heterotypic DENV infection[45]	unknown
Specific sequence	12 possible 2 nd infection sequences; some more pathogenic than others[45]	unknown
Immunity post 1 st infection, homologous	lifetime	Presumed long duration protection against homologous virus
Immunity post - 1 st infection, heterologous	1 – 2 years protection [46]	unknown
Immunity post - 1 st infection, heterologous	Post 1 – 2 years, lifetime sensitization to ADE with 2 nd infection[47]	unknown
Immunity post - 2 nd infection	Lifetime protection	unknown
Viremia	peak enhancement early; duration 2 nd infection shorter than 1 st infection[19]	unknown
Virus in tissues	RNA, viral antigen detectable live virus not[48]	Virus in tissues
Risk factors	Pre-existing health conditions	Pre-existing health conditions
Risk factors: age	Youngest and oldest at greatest risk	Oldest at greatest risk
Attack rates	Controlled by prevalence of 1 st DENV infection antibodies.[47]	No antibody effect observed
ADE with passive Antibody	5 - 11 month-old infants born to DENV-immune mothers[47]	Not observed
Viral pathogenicity	Increases month to month; single mutation controls[49]	Not observed
Vaccine ADE	Dengvaxia raises non-protective (ADE) antibodies, sensitizing non-immunes[16, 17]	Challenge virus produces VAH in vaccinated animals[9, 10, 50]

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