This is temporary review material for *Dangers of COVID-19 Vaccine Associated Enhanced Disease* by Leo Goldstein, June 2021.
https://defyccc.com/vaed

Excerpts

(Agrawal et al. 2016)

"Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus"

"Inactivated MERS-CoV vaccine appears to carry a hypersensitive-type lung pathology risk from MERS-CoV infection that is similar to that found with inactivated SARS-CoV vaccines from SARS-CoV infection."

(Arvin et al. 2020)

"ADE of disease cannot be reliably predicted after either vaccination or treatment with antibodies"

"At present, there are no known clinical findings, immunological assays or biomarkers that can differentiate any severe viral infection from immune-enhanced disease, whether by measuring antibodies, T cells or intrinsic host responses. In vitro systems and animal models do not predict the risk of ADE of disease"

(Cardozo and Veazey 2020)

"Published literature was reviewed to identify preclinical and clinical evidence that COVID-19 vaccines could worsen disease upon exposure to challenge or circulating virus."

"The specific and significant COVID-19 risk of ADE should have been and should be prominently and independently disclosed to research subjects currently in vaccine trials, as well as those being recruited for the trials and future patients after vaccine approval, in order to meet the medical ethics standard of patient comprehension for informed consent."

(Chen et al. 2021)

"This discovery, unfortunately, implies the vulnerability of current vaccines and antibody drugs to new mutations. Our predictions were validated by comparison with more than 1400 deep mutations on the S protein RBD. Our results show the urgent need to develop new mutation-resistant vaccines and antibodies and to prepare for seasonal vaccinations."

"A major potential challenge is an antibody-dependent enhancement, in which the binding of a virus to suboptimal antibodies enhances its entry into host cells. All vaccine and antibody therapeutic developments are currently based on the reference viral genome reported on January 5, 2020."

(Dandekar and Perlman 2005)

"Administration of spike-protein-specific antibodies to uninfected domestic cats or active immunization of domestic cats with recombinant vaccinia virus that expresses spike protein results in an accelerated disease course after infection with FIPV."

(Di Caro et al. 2021)

"More than 12 000 mutations have already been detected in the SARS-CoV-2 sequence, compared with the reference sequence described at the beginning of the outbreak in Wuhan"

"Increasing population immunity through natural infections and immunizations will increase the selection pressure on the virus and probably increase the evolution of new escape mutants."

(Dispinseri et al. 2021)

"The presence of neutralizing antibodies within the first weeks from symptoms onset correlates with time to a negative swab result (p = 0.002), while the lack of neutralizing capacity correlates with an increased risk of a fatal outcome (p = 0.008). Neutralizing antibody titers progressively drop after 5-8 weeks but are still detectable up to 8 months in the majority of recovered patients regardless of age or co-morbidities, with IgG to spike antigens providing the best correlate of neutralization. Antibody responses to seasonal coronaviruses are temporarily boosted, and parallel those to SARS-CoV-2 without dampening the specific response or worsening disease progression."

(EMA re-Pfizer 2021)

"At the data cut-off of 14 Nov-20, 10-14 weeks safety data are available. Thus, long-term safety is included as missing information"

"Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) should be taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and a post authorisation safety study."

"Important potential risks | Vaccine-associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD)"

"Studies to monitor potential safety concerns (autoimmune disorders, VAED) are planned."

"There is a theoretical risk, based on non-clinical data with MERS and SARS vaccines, of vaccine associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), however no cases were identified in clinical studies with COVID-19 vaccines …"

(EMA re-Moderna 2021)

"*Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)"* to be addressed in Phase 3, by the end of 2022

"*Generally, it cannot be foreseen whether potential future mutations of the SARS-CoV-2 virus may lead to a reduced susceptibility to the neutralising antibodies induced by vaccination with mRNA-1273. Therefore, even though the currently available data (non-clinical, clinical, neutralising capacity of antibodies) do not raise a concern at the time being, the possibility of enhanced disease cannot be excluded with certainty. The current version of the RMP lists vaccine-associated enhanced respiratory disease as a safety concern and an important potential risk.*"

"*Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease) should be taken into account. The applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and post-authorisation safety studies.*"

(Eguia et al. 2021)

"We identify human sera from the 1980s and 1990s that have neutralizing titers against contemporaneous 229E that are comparable to the anti-SARS-CoV-2 titers induced by SARS-CoV-2 infection or vaccination. We test these sera against 229E strains isolated after sera collection, and find that neutralizing titers are lower against these 'future' viruses"

(FDA re-Guidance 2020)

"Data from studies in animal models administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD)."

(Garber 2020) https://archive.is/Iqs2k

"Coronavirus vaccine developers wary of errant antibodies"

"Concerns persist that COVID-19 vaccines could cause antibody-dependent enhancement, which can potentiate viral entry into host cells and worsen disease."

"There are mounting theoretical concerns that vaccines generating antibodies against SARS-CoV-2 may bind to the virus without neutralizing it. Should this happen, the non-neutralizing antibodies could enhance viral entry into cells and viral replication and end up worsening infection instead of offering protection, through the poorly understood phenomenon of ADE. ADE "is a genuine concern," says virologist Kevin Gilligan, a senior consultant with Biologics Consulting, who advises thorough safety studies. "Because if the gun is jumped, and a vaccine is widely distributed that is disease enhancing, that would be worse than actually not doing any vaccination at all."

The degree of ADE vaccine risk for SARS-CoV-2 is unknown."

"Halstead noted that animals previously infected with one serotype did worse if infected again with a different serotype than if never previously infected at all."

"Poor-quality antibodies that bind the virus without neutralizing it are one reason vaccine candidates fail, and, in theory, could also cause ADE, delivering virions to host cells."

"Cats vaccinated with spike protein against feline coronavirus died much faster than unvaccinated cats and carried more anti-spike antibodies, implicating ADE. But macaques vaccinated against SARS-CoV-1 did not show enhanced infection or disease."

"Gilligan says some earlier SARS and MERS vaccine candidates didn't advance because of signs of ADE."

(Hellerstein 2020)

"Progress in laboratory markers for SARS-CoV2 has been made with identification of epitopes on CD4 and CD8 T-cells in convalescent blood. These are much less dominated by spike protein than in previous coronavirus infections. Although most vaccine candidates are focusing on spike protein as antigen, natural infection by SARS-CoV-2 induces broad epitope coverage, cross-reactive with other betacoronviruses."

"Subneutralizing antibodies can promote viral entry into cells, including entry into and activation of macrophages and can occur through low-affinity antibodies, cross-reactive antibodies to different strains, or suboptimal titers of neutralizing antibodies."

"Spike accounted for 27% of total responsive CD4 T-cells, with membrane (M) and nucleocapsid (N) proteins accounting for 27% and 11%, respectively. In comparison, spike protein accounted for ~2/3 of reactive CD4 T-cells after previous coronavirus infections in humans"

"The results were even more striking for CD8 T-cells. Spike-reactive CD8 T-cells comprised only 26% and M 22% of the total CD8 responsive cells, while nsp6, ORF3a, and N comprised ~50%. This is very different from prior coronavirus infections, where spike generally contributed ~50%"

"These findings carry a potentially important message for SARS-CoV-2 vaccines. Most current vaccine candidates are focusing on spike protein as the immunizing antigen, but natural infection induces broad epitope coverage in T-cells."

"It would be a public health [nightmare] if immune protection wears off or antibody-dependant enhancement develops and we face recurrent threats from COVID-19 among the immunized."

(Lee et al. 2020)

"In this Perspective, we discuss the possible mechanisms of ADE in SARS-CoV-2 and outline several risk mitigation principles for vaccines and therapeutics."

(Lyons-Weiler 2020)

"SAR-CoV-2 spike proteins, and all other SARS-CoV-2 proteins, immunogenic epitopes in each SARS-CoV-2 protein were compared to human proteins in search of high local homologous matching. Only one immunogenic epitope in a SARS-CoV-2 had no homology to human proteins."

"In SARS, a type of "priming" of the immune system was observed during animal studies of SARS spike protein-based vaccines leading to increased morbidity and mortality in vaccinated animals who were subsequently exposed to wild SARS virus."

(Fierz and Walz 2020)

"It is actually typical for the immune system to respond, like the brain, to what it already knows, a phenomenon that has been observed in many infections with closely related viruses and has been termed "original antigenic sin.""

"Depending on the antigen against which antibodies are made in a first infection or immunization, in a second immunization with a different antigen of influenza, the immune system is only boosting the antibodies against the old antigen and does not recognize the new antigen."

"Wang et al. showed that antibodies against different epitopes of spike glycoprotein either protect or enhance SARS-CoV infections in a Vero E6 cell line as well as in vivo in macaques. Antibodies produced to the epitopes S597–603 and S604–625 strongly aggravated lung damage in macaques."

"A similar finding was reported in a mouse model with four different SARS-CoV vaccines when after a post-vaccination viral challenge the viral load was lower compared to controls, but all mice showed histopathological changes in the lungs with eosinophil infiltration, which did not occur in controls that had not been vaccinated."

"The exact pathogenic mechanism of possible ADE in COVID-19 is not yet known."

(Gao et al. 2003)

"adenoviral delivery of codon-optimised SARS-CoV strain Urbani structural antigens spike protein S1 fragment, membrane protein, and nucleocapsid protein to induce virus-specific broad immunity in rhesus macaques" – now somebody decided that only S-protein is enough for humans"

(Lawrensia et al. 2020)

"The first possible hypothesis is that PIMS-TS is an immunologically mediated pathogenesis or a post-infectious process caused by non-neutralizing IgG antibody through antibody-dependent enhancement (ADE). The reported cases of PIMS-TS emerged after the peak of SARS-CoV-2 infection in some countries. They found that most patients were more often had a positive test for antibody to SARS-CoV-2 than for the virus using nasopharyngeal RT-PCR, which raises the possibility of the involvement of acquired immunity aberrant development. This evidence is supported by the finding from a large multicentre observational study among 78 children … . This result supports the evidence that PIMS-TS might not be an acute COVID-19 infection, but it is more likely a post-immunological reaction."

(NBC News 2021)

"Every year, you need to go to get your flu vaccine," Bourla said. "It's going to be the same with Covid. In a year, you will have to go and get your annual shot for Covid to be protected."

(Ricke 2021)

"Antibody-dependent enhancement (ADE) may be involved in the clinical observation of increased severity of symptoms associated with early high levels of SARS-CoV-2 antibodies in patients. Infants with multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 may also have ADE caused by maternally acquired SARS-CoV-2 antibodies bound to mast cells. … SARS-CoV-2 antibodies bound to Fc receptors on macrophages and mast cells may represent two different mechanisms for ADE in patients."

"Vaccine-associated enhanced disease (VAED) can result when there are multiple circularizing serotypes of virus or when the virus uses antibodies for expanded host cell trophism of phagocytic immune cells."

"Given past data on multiple SARS-CoV-1 and MERS-CoV vaccine efforts have failed due to ADE in animal models, it is reasonable to hypothesize a similar ADE risk for SARS-CoV-2 antibodies and vaccines. ADE

risks may be associated with antibody level (which can wane over time after vaccination) and also if the antibodies are derived from prior exposures to other coronaviruses"

(Rothan and Byrareddy 2021)

"The ADE was implicated in a respiratory syncytial virus (RSV) vaccine trial when the vaccinated children carried high titers of non-neutralizing antibodies. Approximately, 80% of the children immunized against RSV ended up hospitalized … Macaques received vaccinia virus expressing SARS-CoV-1 spike exhibit acute lung injury upon viral challenge than controls and the blockade of FcγR reduced such effects. Hamsters vaccinated with SARS-CoV-1 spike protein were potentially protected from SARS-CoV-1 infection but showed evidence of developing anti-sera that facilitated ACE2-independent virus entry. Cats vaccinated with spike protein against feline coronavirus died much faster than unvaccinated cats and carried more anti-spike antibodies, implicating ADE. Four different SARS-CoV-1 vaccines developed for human use were tested in mice. All vaccines induced immune response and protection against virus infection but Th2-type immunopathology suggesting hypersensitivity to SARS-CoV components was observed. "

"there is a possible role of SARS-CoV-2 non-specific antibodies in the development of MIS-C disease via antibody-dependent enhancement (ADE)"

(Vatti et al. 2017)

"Original antigenic sin: A comprehensive review"

"Original antigenic sin explains the failure of the immune system to generate an immune response against related antigens. In the original antigenic sin a prior exposure to an antigen leads to an ineffective to no response to a related antigen."

"In the case of vaccines, if we only immunize to a single strain or epitope, and if that strain/epitope changes over time, then the immune system is unable to mount an accurate secondary response. In addition, depending of the first viral exposure the secondary immune response can result in an antibody-dependent enhancement of the disease or at the opposite, it could induce anergy. Both of them triggering loss of pathogen control and inducing aberrant clinical consequences."

"Paradoxically, if "original antigenic sin" scenario would occur with each secondary infection, it would be more dangerous to have been heterologously inoculated than not to be inoculated at all which would argue against vaccination principle."

(Weisblum et al. 2020)

"SARS-CoV-2 S variants that resist commonly elicited neutralizing antibodies are now present at low frequencies in circulating SARS-CoV-2 populations."

(Wan and et al. 2020)

"Antibody-dependent enhancement (ADE) of viral entry has been a major concern for epidemiology, vaccine development, and antibody-based drug therapy."

"Antibody-dependent enhancement (ADE) of viral entry has been observed for many viruses. It was shown that antibodies target one serotype of viruses but only subneutralize another, leading to ADE of the latter viruses."

"ADE can lead to worsened symptoms in secondary viral infections, causing major concerns for epidemiology. ADE is also a major concern for vaccine design and antibody-based drug therapy, since antibodies generated or used in these procedures may lead to ADE. ADE has been observed in coronaviruses for decades, but the molecular mechanisms are unknown."

(Wang et al. 2014)

"Results from infectivity assays indicate that SARS-CoV ADE is primarily mediated by diluted antibodies against envelope spike proteins rather than nucleocapsid proteins. We also generated monoclonal antibodies against SARS-CoV spike proteins and observed that most of them promoted SARS-CoV infection. Combined, our results suggest that antibodies against SARS-CoV spike proteins may trigger ADE effects. The data raise new questions regarding a potential SARS-CoV vaccine …"

"We also noted that diluted anti-sera against SARS-CoV promotes SARS-CoV infection, and that this phenomenon is significantly mediated by anti-S antibodies."

"Our data indicate that treatment with anti-sera collected from SARS-CoV patients and diluted 1000- to 2000-fold resulted in increased virus infectivity and CPE compared to treatment with 10-fold diluted anti-sera"

*"**Antibody-dependent SARS-CoV enhancement is mediated by anti-spike antibodies**" – section heading*

"another research team has suggested that SARS-CoV subunit vaccines may induce neutralization and/or partial ADE effects via B lineage cells. In a separate report describing similar results, the researchers suggested that vaccine-induced anti-spike antibodies against trimeric S proteins may mediate the ADE of SARS-CoV-pseudotyped virus entry into FcR-expressing cells"

(Wang and et al. 2016)

"Severe acute respiratory syndrome (SARS) is caused by a coronavirus (SARS-CoV) and has the potential to threaten global public health and socioeconomic stability. Evidence of antibody-dependent

enhancement (ADE) of SARS-CoV infection in vitro and in non-human primates clouds the prospects for a safe vaccine."

"In this study, we reported for the first time that a SARS-CoV inactivated vaccine could induce ADE and lung pathology in experimental rhesus monkeys."

"in persons infected by SARS-CoV, enhancing antibodies and neutralizing antibodies may partly counteract each other's functions."

(Wang et al. 2021)

*"**Vaccine-escape and fast-growing mutations**"*

"We have predicted vaccine escape mutations that are not only fast-growing but also can disrupt many existing vaccines. … the mutations on the S protein RBD tend to disrupt the existing antibodies and vaccines and increase the transmission and infectivity of SARS-CoV-2.

(Wodarg and Yeadon 2020)

"In some viruses, if a person harbors a non-neutralizing antibody to the virus, a subsequent infection by the virus can cause that person to elicit a more severe reaction to the virus due to the presence of the non-neutralizing antibody. This is not true for all viruses, only particular ones. This is called Antibody Dependent Enhancement (ADE), and is a common problem with Dengue Virus, Ebola Virus, HIV, RSV, and the family of coronaviruses. In fact, this problem of ADE is a major reason why many previous vaccine trials for other coronaviruses failed. Major safety concerns were observed in animal models. If ADE occurs in an individual, their response to the virus can be worse than their response if they had never developed an antibody in the first place. This can cause a hyperinflammatory response, a cytokine storm, and a generally dysregulation of the immune system that allows the virus to cause more damage to our lungs and other organs of our body. … There are many studies that demonstrate that ADE is a persistent problem with coronaviruses in general, and in particular, with SARS-related viruses. ADE has proven to be a serious challenge with coronavirus vaccines, and this is the primary reason many of such vaccines have failed in early in-vitro or animal trials."