(STUDY) Why so many vaccinated people are getting sick: Antibody Dependent Enhancement (ADE)

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According to studies:

- ADE can make vaccinated people more susceptible to serious infection from the virus
- "ADE may be a concern" for those who have been vaccinated for Covid-19
- With ADE, after people get vaccinated for an initial virus, infection by a subsequent variant or strain of the virus can result in "increased viral replication and more severe disease, leading to major safety risks"
- ADE can also "occur when neutralizing antibodies (which bind the virus and stop it from causing infection) are present at low enough levels that they don't protect against infection. Instead, they can form immune complexes with viral particles, which in turn leads to worse illness"
- This concern was initially described by some scientists who were subsequently banned from media platforms that incorrectly claimed the scientists were disseminating disinformation
- Study scientists suggest the answer is to create a new vaccine

In a new study in the *Journal of Infection*, scientists explain one likely reason why so many vaccinated people are getting sick: a dangerous phenomenon called Antibody Dependent Enhancement or ADE.

Despite the fact that multiple medical authorities predicted, told us, and hoped, ADE would not impact Covid-19 vaccines, data from the study indicates it has done just that.

According to the new study, data suggests that the Covid-19 vaccines originally appeared to provide an overall benefit in fighting the virus. However, when it comes to one of the newer iterations of Covid, the Delta variant, the vaccines appear to facilitate infection displaying "a strikingly increased affinity" for the virus' trademark spike protein.

The scientists conclude that "ADE may be a concern" for those who have been vaccinated for Covid-19.

Read the study here.

According to scientific study, the ADE risk was well known prior to the Covid-19 vaccines being allowed on the market.

"One potential hurdle for antibody-based vaccines and therapeutics is the risk of exacerbating COVID-19 severity via antibody-dependent enhancement (ADE)," explained a study in Nature. "ADE can increase the severity of multiple viral infections, including other respiratory viruses such as respiratory syncytial virus (RSV) and measles."

Scientists say that with ADE, after people get vaccinated for an initial virus, infection by a subsequent variant or strain of the virus can result in "increased viral replication and more severe disease, leading to major safety risks."

"Non-neutralizing antibodies generated by past infection or vaccination fail to shut down the pathogen upon re-exposure. Instead, they act as a gateway by allowing the virus to gain entry and replicate in cells that are usually off limits... That, in turn, can lead to wider dissemination of illness, and over-reactive immune responses that cause more severe illness," according to scientists.

An article in MedPage (prior to the new study) dismissed concerns about ADE, but noted it "can also occur when neutralizing antibodies (which bind the virus and stop it from causing infection) are present at low enough levels that they don't protect against infection. Instead, they can form immune complexes with viral particles, which in turn leads to worse illness."

On the other hand, most scientific studies on this topic say those who have recovered from Covid-19 have natural immunity that does not display the same problem, and appears to be superior to that, so far, of that provided by the vaccines.

Nonetheless, the Centers for Disease Control (CDC) and many public health officials are pressing for more people to get vaccinated, including those who have been previously-infected with Covid. (Numerous studies suggest there is no benefit to recovered patients getting vaccinated.) The health officials state that the vaccinated patients who are getting Covid are getting milder forms than they would have if they had not been vaccinated. However, that is a case-by-case assumption and is impossible to prove.

In Israel, health officials say that only 1% among Covid infections in the latest wave are among those previously infected with Covid. The other 99% are among unvaccinated and not previously-infected, and among fully-vaccinated.

- Covid-19 Natural Immunity: The Definitive Summary
- Covid-19 Vaccine Concerns Summary
- Covid-19 Vaccine Analysis: Common Adverse Events
- Covid-19 Origins: Separating Rumor from Fact (WATCH)
- Report a Possible Vaccine Adverse Event,

According to the new study, the solution to the current ADE problem is to invent a new, updated version of the vaccine.

Children's Hospital of Philadelphia (which accepts funding from the vaccine industry) reports the following about ADE:

A major goal of antibodies is to bind to the pathogen and prevent it from infecting, or entering, a cell. Antibodies that prevent entry into cells are called neutralizing antibodies. Many vaccines work by inducing neutralizing antibodies. However, not all antibody responses are created equal. Sometimes antibodies do not prevent cell entry and, on rare occasions, they may actually increase the ability of a virus to enter cells and cause a worsening of disease through a mechanism called antibody-dependent enhancement (ADE).

What is ADE?

ADE occurs when the antibodies generated during an immune response recognize and bind to a pathogen, but they are unable to prevent infection. Instead, these antibodies act as a "Trojan horse," allowing the pathogen to get into cells and exacerbate the immune response.

Is ADE caused by vaccines?

On a few occasions ADE has resulted from vaccination:

- *Respiratory syncytial virus (RSV) — RSV is a virus that commonly causes pneumonia in children. A vaccine was made by growing RSV, purifying it, and inactivating it with the chemical formaldehyde. In clinical trials, children who were given the vaccine were more likely to develop or die from pneumonia after infection with RSV. As a result of this finding, the vaccine trials stopped, and the vaccine was never submitted for approval or released to the public.*
- *Measles — An early version of measles vaccine was made by inactivating measles virus using formaldehyde. Children who were vaccinated and later became infected with measles in the community developed high fevers, unusual rash, and an atypical form of pneumonia. Upon seeing these results, the vaccine was withdrawn from use, and those who received this version of the vaccine were recommended to be vaccinated again using the live, weakened measles vaccine, which does not cause ADE and is still in use today.*

A more recent example of ADE following vaccination comes from dengue virus:

- *Dengue virus — In 2016, a dengue virus vaccine was designed to protect against all four serotypes of the virus. The hope was that by inducing immune responses to all four serotypes at once, the vaccine could circumvent the issues related to ADE following disease with dengue virus. The vaccine was given to 800,000 children in the Philippines. Fourteen vaccinated children died after encountering dengue virus in the community. It is hypothesized that the children developed antibody responses that were not capable of neutralizing the natural virus circulating in the community. As such, the vaccine was recommended only for children greater than 9 years of age who had already been exposed to the virus.*

Should I be concerned that my child will develop ADE after receiving a vaccination?

Today's routinely recommended vaccines do not cause ADE. If they did, like those described above, they would be removed from use. Phase III clinical trials are designed to uncover frequent or severe side effects before a vaccine is approved for use.

Read more on ADE here.

Read more from the new study below:

Antibody dependent enhancement (ADE) of infection is a safety concern for vaccine strategies. In a recent publication, Li et al. (Cell 184 :1-17, 2021) have

reported that infection-enhancing antibodies directed against the N-terminal domain (NTD) of the SARS-CoV-2 spike protein facilitate virus infection in vitro, but not in vivo. However, this study was performed with the original Wuhan/D614G strain. Since the Covid-19 pandemic is now dominated with Delta variants, we analyzed the interaction of facilitating antibodies with the NTD of these variants. Using molecular modelling approaches, we show that enhancing antibodies have a higher affinity for Delta variants than for Wuhan/D614G NTDs. We show that enhancing antibodies reinforce the binding of the spike trimer to the host cell membrane by clamping the NTD to lipid raft microdomains. This stabilizing mechanism may facilitate the conformational change that induces the demasking of the receptor binding domain. As the NTD is also targeted by neutralizing antibodies, our data suggest that the balance between neutralizing and facilitating antibodies in vaccinated individuals is in favor of neutralization for the original Wuhan/D614G strain. However, in the case of the Delta variant, neutralizing antibodies have a decreased affinity for the spike protein, whereas facilitating antibodies display a strikingly increased affinity. Thus, ADE may be a concern for people receiving vaccines based on the original Wuhan strain spike sequence (either mRNA or viral vectors). Under these circumstances, second generation vaccines with spike protein formulations lacking structurally-conserved ADE-related epitopes should be considered.The aim of the present study was to evaluate the recognition of SARS-CoV-2 Delta variants by infection enhancing antibodies directed against the NTD. The antibody studied is 1054 (pdb file #7LAB) which has been isolated from a symptomatic Covid-19 patient[1]. Molecular modelling simulations were performed as previously described[2]. Two currently circulating Delta variants were investigated, with the following mutational patterns in the NTD :

- - G142D/E154K (B.1.617.1)
- - T19R/E156G/del157/del158/A222V (B.1.617.2)

Each mutational pattern was introduced in the original Wuhan/D614G strain, submitted to energy minimization, and then tested for antibody binding. The energy of interaction (ΔG) of the reference pdb file #7LAB (Wuhan/D614G strain) in the NTD region was estimated to -229 kJ/mol^{-1}. In the case of Delta variants, the energy of interaction was raised to -272 $kJ.mol^{-1}$(B.1.617.1) and -246 $kJ.mol^{-1}$ (B.1.617.2). Thus, these infection enhancing antibodies not only still recognize Delta variants but even display a higher affinity for those variants than for the original SARS-CoV-2 strain.The global structure of the trimeric spike of the B.1.617.1 variant in the cell-facing view is shown in Figure 1**A**. As expected, the facilitating antibody bound to the NTD (in green) is located behind the contact surface so that it does not interfere with virus-cell attachment. Indeed, a preformed antibody-NTD complex could perfectly bind to the host cell membrane. The interaction between the NTD and a lipid raft is shown in Figure 1**B**, and

a whole raft-spike-antibody complex in Figure 1**C**. Interestingly, a small part of the antibody was found to interact with the lipid raft, as further illustrated in Figures 1**D-E**. More precisely, two distinct loops of the heavy chain of the antibody encompassing amino acid residues 28-31 and 72-74, stabilize the complex through a direct interaction with the edge of lipid raft (Figure 1**F**). Overall, the energy of interaction of the NTD-raft complex was raised from -399 kJ.mol^{-1} in absence of the antibody to -457 kJ.mol^{-1} with the antibody. By clamping the NTD and the lipid raft, the antibody reinforces the attachment of the spike protein to the cell surface and thus facilitates the conformational change of the RBD which is the next step of the virus infection process[2].

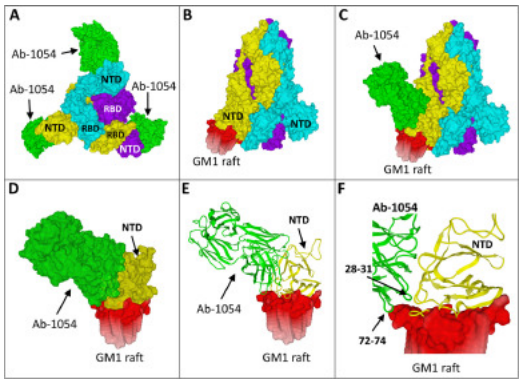

Figure 1Infection enhancing antibodies recognize the NTD of Delta variants. A. Molecular model of the Delta B.1.617.1 spike trimer as viewed from the host cell surface (chains A, B and C in cyan, yellow and purple, respectively), with the NTD and RBD of each chain indicated. The 1054 antibody is in green. **B.** Spike trimer with the B subunit bound to a lipid raft (with 6 ganglioside GM1 molecules). **C.** Trimolecular [spike-antibody-raft] complex. **D.** Focus on the NTD-antibody complex bound to the lipid raft. **E.** Secondary structures of the NTD (yellow) and the antibody (green) bound to lipid raft gangliosides. **F.** The 1054 antibody clamps the NTD and the edge of the lipid raft.

About Sharyl Attkisson

Emmy-Award Winning Investigative Journalist, New York Times Best Selling Author, Host of Sinclair's Full Measure

Comments