

Negative Evidence: Antibody-Dependent Enhancement

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The term “negative evidence” is generally understood to mean “evidence for a theory provided by the nonoccurrence or absence of something.”¹ Absence of evidence is not the same thing. An adverse reaction, for example, might have occurred, but is deliberately being hidden. The lack of expected data is a highly valuable form of negative evidence recognized by astute scientific and legal investigators.^{2,3}

Negative evidence is not uncommon, but it is hard to spot for good reasons. It takes time and effort to produce believable false data. It is much easier and safer for anyone who wants to mislead the public to hide the inconvenient information than to create an elaborate cover-up. Deliberate omission of data is the form of scientific misconduct that is the most difficult to prove.⁴ There are numerous historical precedents involving famous scientists who intentionally omitted relevant data contradicting their favored theories.⁴⁻⁶

Discovery of compelling negative evidence requires not only diligence and commitment but also substantial expertise on the subject. Hence, negative evidence is frequently missed by laypeople, who due to lack of knowledge cannot perceive what should be there but is missing or who don't understand its significance. Such evidence can be easily overlooked when accompanied by ludicrous but distracting claims made by someone not involved in concealing the relevant clues. The subversive tactic of highlighting such claims is called “*muddying the water*” and has been used for centuries.⁷

Given a choice between the obvious liar and a scientist who does not lie—but does not tell the whole truth, the public will select the latter. It will not matter whether a liar was deliberately planted to distract or a mentally unstable attention seeker is being promoted. The existence of a self-evident prevaricator boosts the credibility of the sinister person who is hiding the evidence. The credible-appearing scientist who willfully withholds pertinent information is at least as dangerous as a prevaricating charlatan.

This article examines the negative evidence lurking in the shadows of the COVID-19 vaccination debate, using the controversial case of vaccination-related antibody-dependent enhancement as an example.

Antibody-Dependent Enhancement (ADE)

Antibody-dependent enhancement (ADE) is the puzzling paradox in which virus-specific antibodies, instead of neutralizing the virus, enhance its entry to cells and its replication.⁸ This will result in worsening of the viral disease. This counterintuitive phenomenon has been observed in vitro and in vivo.⁹ It can happen in any scenario in which neutralizing antibodies to the virus are produced, including primary or secondary viral infections and in relation to vaccination.^{8,10,11}

Despite its paradoxical nature, ADE is not rare. It has been initially studied in cases involving flaviviruses, especially dengue virus.¹² However, later research demonstrated its presence during viral invasion by numerous other positive-strand RNA viruses, such as yellow fever virus,¹³ Zika virus,¹⁴ orthomyxoviruses including influenza,¹⁵ retroviruses including human immunodeficiency virus (HIV),¹⁶ orthopneumoviruses (e.g., respiratory syncytial virus, RSV),¹⁷ and coronaviruses including SARS-CoV-1¹⁸ and SARS-CoV-2.¹⁹⁻²²

Even a potential ADE is a big concern for clinicians since it can significantly worsen the clinical course of the viral illness and change the prognosis for the worse.²³ This is especially dangerous since there is a paucity of effective antiviral medication, and treatment of most viral infection involves use of the supportive measures aiding the natural immunity of the patient. With the ADE phenomenon this internal defense becomes a powerful destructive pathogenic mechanism that can result in severe morbidity and mortality. Further studies also demonstrated that the ADE can even interfere with the use of antiviral immunoglobulins as therapy against viral infection.²⁴

Vaccine-related Antibody-Dependent Enhancement (VADE)

Vaccine-related antibody-dependent enhancement (VADE) is a specific type of ADE that occurs when the virus invasion enhancing antibodies are created in the setting of vaccination. As noted by Xu et al., **VADE appears to be an unavoidable problem in vaccine development.**²⁵

Indeed, in the past VADE has been described during vaccinations for: RSV,²⁶ measles,²⁷ and again most famously for dengue fever.²⁸ Disturbingly, vaccines against a precursor of COVID-19 caused by SARS-CoV-1, which contained inactivated virus²⁹ or nucleocapsid protein³⁰ have elicited VADE in animal models.

VADE should be distinguished from the “**leaky/imperfect vaccine**” phenomenon. In their 2015 paper Read et al. demonstrated, based on their studies of Marek's disease, that vaccines that do not prevent transmission (a.k.a. “leaky vaccines”) can promote the emergence of pathogens capable of eliciting more severe disease in unvaccinated subjects. The leaky vaccine effect is not mediated by antibodies but is a result of viral evolution. It is notable that currently used COVID vaccines do not prevent transmission.³¹

To summarize, in VADE the same type, unchanged, non-mutated virus is being helped by the defective antibodies, instead of being destroyed by them. In the leaky vaccine phenomenon, the mutated, changed virus is unaffected by neutralizing antibodies.

Clinical Significance of VADE

To understand the significance of VADE, it is important to understand that when a vaccinated patient gets infected with the pathogen against which the vaccine was supposed to provide immunity, the following four different scenarios may take place:

- **No Illness.** This is the best, desired outcome. It will occur when the vaccine created such a robust immunity against the pathogens that it is eliminated before it causes any harm.
- **Expected Mild Illness.** In this case, the person may experience some mild symptoms. The clinical picture is much milder than the one of the matched unvaccinated subject infected with same pathogen. This is said to be the case for most respiratory and gastrointestinal infections (e.g., influenza, COVID-19, and rotavirus). These mild symptoms are unavoidable in most cases when the microbial inoculum is large.
- **Unexpected Breakthrough Illness.** Traditionally, this term has been reserved for vaccinated people who get more severely ill, requiring hospitalization or experiencing bad outcomes, such as disease complications (e.g., pneumonia) or death. In this case, the vaccine may not have worked as advertised since it did not induce high enough production of neutralizing antibodies to effectively stop or weaken an infection.
- **Catastrophic VADE.** In this scenario, the antibodies that the vaccine generated **actually help the virus infect greater numbers of cells than it would have on its own.** The antibodies bind to the virus and aid it to get into the cell more easily. The result is frequently much more severe illness than if the person had been unvaccinated.

VADE has a very worrisome clinical implication in general for all vaccines. Any medical intervention that may lead to a cascade of adverse reactions violates the most basic medical tenet of *primum non nocere*. In the specific case of COVID-19, Fashadpour and Taherkhani noted that VADE might lead to especially severe or lethal illness upon infection with SARS-CoV-2 due to the modulation of the immune response toward an excessive inflammatory profile with a cytokine storm and resulting tissue damage.³²

ADE and VADE are neither separate clinical diagnoses nor even *sensu stricto* "side effects," but rather are effect modifiers. They are epidemiological phenomena. All the frontline clinician can do is to suspect that an unusually severe clinical course in a single patient is caused by ADE if the patient is non-vaccinated or by VADE if the patient is vaccinated.

Treatment of ADA/VADE is the same as for any very severe and robust viral infection associated with maladaptive immune responses. Hence one can argue that diagnosis of ADE/VADE is not that clinically significant since it does not change the management. It is however very significant epidemiologically. The significance of VADE is that the intervention (vaccination) instead of improving outcomes actually worsens them.

Why Is Nobody Looking for VADE?

As discussed above, the VADE phenomenon is well known in general, and the concerns about its significance for the

COVID-19 vaccines have been raised by many authors.^{20-22,25,33-34} Logically, any evidence to prove or disprove the existence of COVID vaccine-related VADE (CVADE) should be vigorously sought out by the epidemiologists as well as by basic and clinical researchers. Such efforts should have resulted by now in publication of numerous robust epidemiological and research studies, meta-analyses, and case reports, and the establishment of registries. There should be comprehensive entries on these subjects in medical textbooks and in the clinical decision support modules (CDSM) of electronic health records.

Strangely enough, nothing of the sort is happening. On the contrary, there is unexpected asymmetry here. There are plenty of layman-directed posts about CVADE by self-proclaimed "science educators."³⁵⁻³⁷ Those articles offer platitudinous reassurances that CVADE is not a problem. However, they either provide no references or ironically quote research articles that contradict this optimism.³³

At the same time, there is unusual silence by the authorities and mainstream medical community not only about VADE but even about the rate of any type of COVID-19 infections among vaccinated patients. This is so unusual that even the mainstream press started to report on it. In December 2021, an investigative journalist, Ian Hodgson, authored an article in *Tampa Bay Times* entitled "Why won't Florida, CDC release state's breakthrough COVID data?"³⁸ Hodgson reported that for several months both Florida and CDC officials have been refusing requests by his newspapers and other media to release data indicating how many vaccinated Floridians have been infected, hospitalized, or died of COVID-19. According to this reporter, the official reasons for the refusal were "privacy concerns," which legal experts have deemed to be misplaced.³⁸

This information ban is not limited to Florida. A search for CVADE on the CDC webpage performed in late December 2021 produced surprisingly scarce results.³⁹ There is no extensive monograph on this subject there, an irregularity for this website, which is typically full of detailed entries on all things COVID.

This pervasive informational embargo on the stratified data related to breakthrough infections and VADE explains the lack of the epidemiological studies dealing with these matters. Epidemiologists need access to all the data from the large public databases to analyze them statistically. Alternately, they have to receive at least some pertinent datapoints to construct imputational models.⁴⁰ Lack of such access precludes any type of serious epidemiological study.

Despite its enormous theoretical significance, CVADE remains poorly examined by basic science researchers. There was a single "consensus conference" on CVADE attended by the leading basic scientists in March 2020.⁴¹ It appears to have been an ostentatious formality and was not followed by anything substantive. There is a surprising shortage of original basic research papers on CVADE. Moreover, there was a paucity of such research in the early days of vaccine development, when such inquiries should be conducted. Instead, we have very few peculiar late studies like the one published in September 2021 by Maemura et al. with made-to-order reassuring results.⁴² Doing a few animal studies when millions of humans are already vaccinated and boosted is clearly too little, too late.

It is important to note that this regrettable situation does not necessarily reflect the lack of desire to conduct such research by academic researchers. Lay people are unaware that

academic scientists are not free to pursue any research they find personally relevant. There is no magical pool of “free research money” available to them from their institutions. Academicians worldwide can conduct only research projects that are funded through a governmental grant system, such as National Institutes of Health (NIH) grants in the United States.⁴³ There are privately funded grants, but they are scarce and can be typically used as supplements for the governmental grants. Therefore, if any type of research is deemed to be nonessential by a central agency such as the NIH, it will not be funded by it. Consequently, nothing will be done in this area, since conducting research requires money. It cannot be propelled solely by the enthusiasm and good will of an individual academic scientist.

The field of clinical research and case reporting is similarly barren regarding the data on CVADE. Clinical research is subject to the same type of funding mechanisms as basic research. Hence it is plausible to assume that the same type of obstacles that interfered with the performance of basic research could impede clinical studies as well. Nevertheless, in view of tacit observations that vaccinated people still experience COVID-19 one would expect to see some case reports of at least suspected CVADE. Contrary to such expectations, there are very few such reports. For instance, Indonesian authors reported two patients with a clinical presentation consistent with CVADE after administration of CoronaVac vaccine.⁴⁴ Based on clinical data, the authors theorized that vaccination could cause excessive boosting of the inflammatory process leading to an exaggerated clinical course of the COVID-19 illness. However, beside such singular reports virtually no other clinical paper describes the presence or even the suspicion of CVADE.

Initially the lack of reports may lead to the reassuring conclusion that CVADE is indeed irrelevant. However, examination of the papers reporting on vaccinated patients who developed COVID-19 reveals that this absence is caused by the fact that **no one was looking** for CVADE, even though researchers should be looking for it for theoretical reasons and because it has occurred in similar circumstances.⁴⁵⁻⁴⁷

Few authors are concerned about this strange omission. For instance, Yahi et al. in a 2021 article noted that based upon their research VADE may occur in patients receiving vaccines based on the original Wuhan strain spike sequence, including mRNA or viral-vector vaccines, who were subsequently exposed to a Delta variant.⁴⁶ The authors refer to the research study published by Li et al.,⁴⁸ which confirms their findings. They find it puzzling that to their knowledge VADE reactions to the Delta variants have not been specifically assessed. Furthermore, Yahi et al. postulate that *“possibility of ADE should be further investigated as it may represent a potential risk for mass vaccination during the current Delta variant pandemic.”*⁴⁶

The pharmaceutical industry has responded to those reasonable concerns by immediately dispatching their trusted “fact-checker” Derek Lowe.⁴⁸ Lowe happens to be a high-ranking employee of the pharmaceutical company Novartis, according to his LinkedIn profile.⁴⁹ Unsurprisingly, he has penned what he likely considers to be a blistering criticism of those two solid research papers. He admitted that the *“work appears to be very solid, and represents a great deal of effort,”* but posited that it has to be meaningless since *“people promoting this seem to be rooting for the virus, just so long as it humiliates their enemies and*

proves their own positions to be correct.” He added that those papers are just theoretical musings that must be verified in real life. Ironically, this is precisely what the authors of the papers proposed and were puzzled that no one seems to be willing to do.

This is one of many examples illustrating the tactics of suppressing pertinent information and using the created impression of its absence as “proof” of the preferred narrative. The “debunkers” will first discourage any research of the troublesome subject. Subsequently they will claim that there is simply no data about it, and hence that subject does not exist. The sheer arrogance and the mental gymnastics devoted to hiding the inconvenient evidence is staggering. Yet this method appears to be working since such vigorous attacks discourage scientists from asking the bothersome questions and finding the problematic answers. This results in the paucity of original research dealing with controversial topics.

The scarcity of publications about VADE in the scientific literature naturally translates into very cursory coverage of this subject in core clinical textbooks. For instance, the typically comprehensive evidence-based clinical resource UpToDate (which is used frequently as a Clinical Decision support module in the electronic health record) contains only a tiny paragraph on the CVADE, asserting that this effect was not seen in humans,⁵⁰ contradicting the evidence presented above.⁴⁴ The lack of emphasis on VADE in the clinical textbooks leads to the situation in which frontline clinicians will not pay attention to the potential occurrence of such phenomenon. This creates a vicious circle in which real-world data are overlooked and underreported leading to the lack of impetus for the research community to study VADE.

There is no need for any gargantuan elaborate conspiracy to stop the free flow of information on VADE. All one needs is to disallow access to the centrally controlled governmental database and cut the governmental funding for the research. In the current hierarchical and governmental grant-dependent academic research environment, those two simple manipulations will effectively stop any serious inquiry into an inconvenient matter. Subsequently, the misleading narrative that the subject is either non-existing or irrelevant can be easily created.

Note that the Vaccine Adverse Event Reporting System (VAERS) is by design unhelpful in studying effect modifiers like VADE. VAERS is a spontaneous (or passive) public reporting system, not an ongoing formal clinical trial, and not a formal real-world data (RWD) study such as an active survey or registry. If officialdom really cared about the true outcomes of vaccinations, it would long ago have created a comprehensive formal, epidemiological, multitiered active survey/registry system for vaccine outcomes. The system would use formalized questionnaires, medical records abstracting, and actual laboratory data collection, and would, for example, be structured like the National Health and Nutrition Examination Survey (NHANES). Such a system would use observational study methods to collect and harmonize both subjective and objective data about the outcomes of vaccination. Subsequently, it would aggregate large data sets and analyze identifiable trends or patterns correlating subjective reports with objective data.

VAERS still constitutes a headache for vaccine mandate proponents since passive data are better than no data. But

authorities can excuse disregarding safety signals on the basis that VAERS is a very inaccurate system—because it is. It is telling that no member of officialdom seems interested in creating something better than VAERS.

Conclusions

Why is there such a puzzling lack of robust scientific inquiries into CVADE? Why is there a turtle's pace, not "warp speed"? **The nature of evidence here is strikingly negative.** Wouldn't it be better for the huge army of "science communicators" to have plentiful data to support their assertions about the insignificance of CVADE? It certainly would, if the data were in favor of their assertions. But if the data would contradict their narrative, it would be much better for those "science communicators" (read: vaccination promoters) if the public could not see any evidence.

Does no one really care about CVADE? Or is there somebody who cares about limiting the flow of the data about this subject—and why? This is the essential question to ponder.

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AAPS PRINCIPLES OF MEDICAL POLICY

Medical care is a professional service, not a right. Rights (as to life, liberty, and property) may be defended by force, if necessary. Professional services are subject to economic laws, such as supply and demand, and are not properly procured by force.

Physicians are professionals. Professionals are agents of their patients or clients, not of corporations, government, insurers, or other entities. Professionals act according to their own best judgment, not government “guidelines,” which soon become mandates. Physicians’ decisions and procedures cannot be dictated by overseers without destroying their professionalism.

Third-party payment introduces conflicts of interest. Physicians are best paid directly by the recipients of their services. The insurer’s contract should be only with subscribers, not with physicians. Patients should pay their physician a mutually agreed-upon fee; the insurer should reimburse the subscriber according to the terms of the contract.

Government regulations reduce access to care. Barriers to market entry, and regulations that impose costs and burdens on the provision of care need to be greatly reduced. Examples include insurance mandates, certificate of need, translation requirements, CLIA regulation of physician office laboratories, HIPAA requirements, FDA restrictions on freedom of speech and physicians’ judgment, etc.

Honest, publicly accessible pricing and accounting (“transparency”) is essential to controlling costs and optimizing access. Government and other third-party payment or price-

fixing obscures the true value of a service, which can only be determined by a buyer’s willingness to pay. The resulting misallocation of resources creates both waste and unavailability of services.

Confidentiality is essential to good medical care. Trust is the foundation of the patient-physician relationship. Patient confidences should be preserved; information should be released only upon patient informed consent, with rare exceptions determined by law and related to credible immediate threats to the safety or health of others.

Physicians should be treated fairly in licensure, peer review, and other proceedings. Physicians should not fear loss of their livelihood or burdensome legal expenses because of baseless accusations, competitors’ malice, hospitals’ attempts to silence dissent, or refusal to violate their consciences. They should be accorded both procedural and substantive due process. They do not lose the basic rights enjoyed by Americans simply because of their vocation.

Medical insurance should be voluntary. While everyone has the responsibility to pay for goods and services he uses, insurance is not the only or best way to finance medical care. It greatly increases costs and expenditures. The right to decline to buy a product is the ultimate and necessary protection against low quality, overpriced offerings by monopolistic providers.

Coverage is not care. Health plans deny payment and ration care. Their promises are often broken. The only reliable protection against serious shortages and deterioration of quality is the right of patients to use their own money to buy the care of their choice.