# Review of: "Christ Bearing the Cross: the original antigenic sin of the immune system and its potential role in emerging diseases"

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Rijkers and van Overveld discuss the immunologic phenomenon of original antigenic sin (OAS). Their title suggests they will illuminate the influence(s) of OAS in emerging infectious diseases. In this context, the authors offer brief comments on ndOAS and infections by SARS-CoV-2, RSV, HIV, and dengue.

OAS is an interesting immunobiological phenomenon that has the potential to greatly affect the trajectories of epidemics and pandemics due to infectious agents (particularly certain viruses) that are subject to extensive antigenic variation. Of course, the definition of OAS, like the definitions for many terms used in biomedicine, can vary much like the antigenicity of influenza hemagglutinin (HA) or the SARS-CoV-2 spike protein. In the seminal 1966 study on OAS in connection with immunization against influenza A viruses by Fazekas de St. Groth and Webster [*J. Exp. Med.* Sep 1;124(3):331-45], OAS is introduced and defined as follows:

“Thus it has been known for over 10 yr now that humans vaccinated against influenza produce antibodies against the immunizing antigen, but produce anti- bodies of higher titer against the antigen that was their first childhood experience of influenza, even if that strain happened to be absent from the vaccine …”

A critical but perhaps subtle aspect of this characterization is that titer is a composite variable involving many potential pairings of antibody concentration and effective functional affinity for these antibodies. I say functional affinity instead of single-site or intrinsic affinity, because, for a given number of bivalent IgG antibody molecules able to bind to an antigen, the amount of antibody that binds to antigen, under defined conditions of temperature, pH, ionic strength, and potentially other variables, will depend not only on the intrinsic affinity but also the percentage of cases for which binding is monogamously bivalent. This functional affinity for any given IgG molecule, what many call avidity, will depend not only on the effective valence and intrinsic affinity but also the biophysical properties, such as segmental flexibility, that vary by IgG subclass and influence the probability that both arms can engage simultaneously.

As emphasized by Yewdell and Santos [Cold Spring Harb Perspect Med. 2021 May 3;11(5):a038786] in their detailed analysis of OAS, differences in the precise methods used to assess antibody binding to various strains of a virus or their relevant antigens, can yield considerable variation in the extent to which OAS is evident. Other relevant factors subject to variation that can influence the extent of the OAS phenomenon include the amount of immunogen involved in immunization or infection, the nature and amount of adjuvant present during immunization, and number of immunizations.

The meanings of “sin” in the context of OAS are also subject to variation. My initial sense of the intended meaning was an event or exposure that exerts influence on subsequent behaviors or outcomes. I did not attribute a good-bad valence to the term, as Rijkers and Overveld seem to at times. But, that other meaning for sin is unsurprising and used as well by others in some prior commentaries on OAS.

In that context and in line with the thorough analysis by Yewdell and Santos cited above, I would note that it is generally unwise to assume that all of the selective forces impinging on a molecule, cell type, process, or phenomenon, can be identified by a casual or quick analysis. Yewdell and Santos, for example, discuss a number of effects of the humoral response dominated by antibodies derived from B cell lineages initially elicited in response to an earlier version of a viral antigen. Rijkers and Overveld do not cover all of these potentially relevant aspects of the effects of OAS on fitness.

Overall, the commentary of Rijkers and Overveld addresses a phenomenon investigation of which could prove to be valuable not merely for the guidance it provides to vaccinologists, immunologists, virologists, specialists in infectious disease, physicians more generally, and public health experts in minimizing the harms of epidemics and pandemics but also for the deeper insights into the seemingly inexhaustible intricacies and subtleties that have shaped the evolution of immune mechanisms. In that regard, I would view this contribution as providing an accessible introduction to OAS, which is relevant to a number of biomedical fields.