Is Measurement of Systemic IgG Antibodies the Wrong Way to Assess COVID-19 Vaccine Effectiveness for Breakthrough Infections?

TO THE EDITOR:

Although vaccination against SARS-CoV-2 has substantially reduced severe disease, there have been many milder breakthrough infections. One possible explanation for these seemingly paradoxical infections is that IgG antibodies initiated by systemic vaccination provide little protection to the mucosal tissue of the nose and throat. There are two humoral antibody immune systems: the systemic that originates from bone marrow and produces largely monomeric IgG and the mucosal/gastrointestinal associated lymphoid tissue (MALT/GALT) (1) that produces largely dimeric IgA and dominates the glandular tissue of the nose and throat. Actually, the number of IgA-producing plasma cells exceeds the number of systemic plasma cells (1).

The systemic system does not necessarily transmit an immunological message to the MALT/GALT when it is immunized by vaccination. On the other hand, when a respiratory virus enters the nasal passages with natural infection, mucosal immune responses are induced in the nasopharynx, both across the nasal epithelium and via the tonsils and adenoids (2). Moreover, it is likely such infection is accompanied by a systemic response since the stroma beneath is dominated by IgG cells (1). In those with normal immunity who are fully vaccinated, infection by SARS-CoV-2 is neutralized in the blood stream and tissue fluids and does not cause lung infection. But in many vaccinated people, the virus can still induce nasal cold-like symptoms, with headache, fatigue, and even low-grade fever—sometimes severe.

In the Oxford University study, SARS-CoV-2 viral RNA was detected in nose swabs from all rhesus macaques whether or not vaccinated, and no difference was found between vaccinated and unvaccinated animals from nasal tissue, although the vaccinated animals showed no pneumonia in the lower respiratory tract while the control animals exhibited disease (3). This information suggests that vaccinated persons who are exposed may carry the live virus for several days but not have systemic disease. Evidence indicates mucosal immunity protects from SARS-CoV-2 infection: Anti-SARS-CoV-2 nasal antibodies, and particularly, anti-receptor binding domain (RBD) IgA correlated with the resolution of systemic disease symptoms, and the viral load was negatively correlated with anti-S RBD mucosal antibody (2). Moreover, IgA neutralizing antibodies in serum and saliva were shown to contribute to a much larger extent to virus neutralization in early infection, as compared to IgG (4). Also, after the appearance of the more infectious viral strains, persons with natural infection were between 32.5- and 19.8-fold lower for reinfection than those who were previously not infected and not vaccinated, while persons who were only vaccinated but never infected were 4.5- to 6.2-fold lower than unvaccinated with no previous infection. Besides, there was little difference in reinfection among those previously infected and vaccinated and those previously infected without vaccination (5). It follows that natural infection through the nasal system provides better nasal protection than systemic vaccination alone, even though 2 doses of RNA vaccines have been shown to produce systemic IgG levels as high as convalescence serum (6, 7).

It appears that immunization by systemic vaccination is communicated to the MALT/GALT, but to what degree is unclear. Well-studied polio virus also enters through the mucosal tissue and may provide an example: Although intramuscular systemic inactivated polio vaccine (IPV) is recommended for polio in the United States, and it induces immunity in the mucosal system, IPV induces less mucosal immunity than the oral polio vaccine (OPV) that directly interacts with mucosal tissue (8, 9), even though IPV induced higher serum antibody level (9). Besides, it was shown that mucosal IgA class neutralizing antibodies and titers in stool were as high as in serum after OPV and were superior to IPV (10). Moreover, IgA dimers, the primary form in the nasopharynx, are on average about 7 to 15 times more potent than IgG at neutralizing SARS-CoV-2 (11, 12).

OPV is the vaccine of choice for the poliomyelitis eradication because it induces both a systemic and mucosal immune response. Because OPV is an inactivated live virus, mutations cause emergence of vaccine-derived polioviruses strains that can result in vaccine-associated paralytic poliomyelitis (VAPP), with an estimated one case of VAPP per 2.9 million doses (13). As a result, IPV is recommended by the CDC. It seems that multiple doses of SARS-CoV-2 systemic vaccine may produce greater mucosal immunity. Two doses of IPV are >90% effective against polio and 3 doses are 99% to 100% effective (14). Four doses of polio IPV are recommended by the CDC. Thus, boosters may be a key (15) for reducing breakthrough infection.

If eradication is possible, it requires widespread vaccination over many years. It took 100 years to eradicate smallpox and 30 years to eradicate polio. Moreover, neither of these viruses are as infectious as SARS-CoV-2, with a rate similar to measles. In the United States, measles vaccine was introduced in 1963 and about 1300 cases of measles were reported in 2019, most related to unvaccinated persons. In any case, measurement of IgG antibodies in blood, as is commonly performed for those wishing to ascertain their immune status and in vaccine studies, will likely not provide sufficient information to assess breakthrough infection status.

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