Science Review for Medical Professionals on Vaccine Response Modifying Factors

Numerous COVID-19 vaccines are being tested around the world, and billions of people will receive a COVID-19 vaccine in hopes of returning some normalcy to their lives and communities. Medical professionals may need to have meaningful discussions with their patients to help them have the best possible outcomes and to allay concerns they may have. We present this information from peer-reviewed publications to educate providers on experiences from other vaccines to safely get the best results and to summarize the available scientific evidence on factors that providers may want to consider when advising patients. In addition to providing patients with information about vaccines, we can also aim to help patients build resilient immunity through a healthy lifestyle and optimal nutrition. When our immune systems embody resilience, we have rapid, controlled responses to immune threats and reduce the inflammatory collateral damage to our bodies.

Vaccine 101

According to the Centers for Disease Control and Prevention (CDC), "Vaccines help develop immunity by imitating an infection. This type of infection, however, almost never causes illness, but it does cause the immune system to produce T-lymphocytes and antibodies. Afterward the body is left with a supply of 'memory' T-lymphocytes, as well as B-lymphocytes that will remember how to fight that disease in the future. There are several types of vaccines commonly used at present:

- **"Live, attenuated vaccines (e.g. MMR).** These vaccines contain a version of the living virus or bacteria that has been weakened so that it does not cause serious disease in people with healthy immune systems. People with weakened immune systems may not be able to receive these vaccines.
- **"Inactivated vaccines (e.g. polio).** These vaccines are made by inactivating or killing the bacteria or virus during manufacture. They often require multiple doses to be effective.
- **"Toxoid vaccines (e.g. diphtheria/tetanus).** These vaccines prevent diseases caused by bacteria that produce toxins in the body. Weakened toxins are called toxoids. When the immune system receives a vaccine containing a toxoid, it learns how to fight off the natural toxin.
- **"Subunit vaccines (e.g. pertussis).** These vaccines contain antigenic fragments of the virus or bacteria, rather than the whole organism.
- **"Conjugate vaccines (e.g. *Haemophilus influenzae* type B [Hib]).** These vaccines work against bacteria that have antigens with an outer coating of sugar-like substances called polysaccharides, which can make it harder for the immune system to recognize the infection. Conjugate vaccines are effective for these types of bacteria because they connect (or conjugate) the polysaccharides to antigens that the immune system responds to very well."[1]

For further background information on vaccines see link: https://www.cdc.gov/vaccines/hcp/conversations/downloads/vacsafe-understand-color-office.pdf

Demographic factors

While we might not have specific data related to factors that influence a COVID-19 vaccine for years, responses to other viral vaccines (such as flu) may be valuable in helping forecast demographic factors when it comes to efficacy and adverse effects.

Age

In general, vaccines are less effective in older people; unfortunately, they are some of the most vulnerable to COVID-19.[2] In the well-studied influenza vaccine, age-related declines in immune function (immunosenescence) and age-related chronic inflammation (inflammaging) may be responsible for a poorer response in older adults.[3,4] Older people may need higher vaccine doses or the addition of adjuvants to get adequate responses, while other mechanisms are being explored to increase the efficacy in this population.[2]

Sex
Females tend to have higher antibody responses to influenza vaccination, but they also experience more adverse reactions.[5] Reactions such as muscle pain, redness at injection site, and systemic reactions such as fever, chills, nausea, headaches, and body aches are more frequent among females.[5]

Obesity
The chronic inflammation associated with obesity has systemic implications on immunity.[6] In a study involving 1,042 adults who received an influenza vaccine, those with obesity had double the risk of developing influenza or influenza-like illness compared with those with healthy weight, despite both groups' appearing to respond equally in terms of antibodies in their blood.[7] A possible explanation of the reduced effectiveness of influenza vaccines in this population is due to inferior T cell function. It has been shown that T cells from influenza-vaccinated adults with obesity are less activated when stimulated with vaccine strains of influenza.[8]

Malnourished and frail
Evidence is limited in this population, but several small studies suggest vaccine-induced responses are not diminished by malnourishment or frailty.[9,10] However, it has also been shown that protein malnutrition may cause weak vaccine responses that are ameliorated by supplementing protein.[11]

Lifestyle factors
Exercise
Exercise prior to flu and meningococcal vaccination does not appear to be beneficial or harmful.[12,13] However, one small study in participants over 62 years showed those who intensely exercised over 60 minutes per week increased their antibody response to flu vaccine when compared to sedentary controls.[14]

Mood
One small study involving adults aged 65-85 years receiving influenza vaccination observed that positive mood on the day of flu vaccination was associated with higher antibody responses 16 weeks postvaccination.[15]

Chronic psychological stress
There is some evidence showing that adults or older individuals with chronic psychological stress had lower antibody responses after flu vaccination.[16,17,18] Similar effects were seen in young adults in regards to hepatitis B and meningococcal vaccine.[13] Acceptance of stressful situations rather than coping with substance use also increases antibody responses in this population.[13] Children with high stress levels and low self-esteem have lower responses to rubella and pneumococcal vaccine.[13]

Smoking and alcohol
The influence of cigarette smoking on the efficacy of influenza vaccination is largely unknown. A 1999 study in Dutch patients over 60 years old found smoking had no clinical significance for preventing infection.[19] Alcohol doesn't appear to affect vaccine responses to hepatitis A or B but may negatively impact pneumococcal vaccination.[13]

Sleep
Shortened sleep in the week of hepatitis B vaccine lowers antibody responses; however, sleep quality does not.[13] Sleep deprivation the night following hepatitis A vaccine lowers responses, and longer slow-wave sleep improves it.[13]

Toxin exposure
Exposure to lead in children does not appear to reduce antibody responses to tetanus, though arsenic exposure decreases mumps vaccine antibodies.[13] Exposure to polychlorinated biphenyls (PCBs) and dioxins reduces measles and mumps vaccine responses.[13]

Micronutrients
Selenium
Selenium is a nutrient closely tied to immune and antioxidant functions. Selenium is involved in the proliferation of T-cells and the chemicals they use to fight off infections.[20,21] Selenium can also help shift macrophages to the anti-inflammatory M2 phenotype.[22] Selenium supplementation in those with low intake has been shown to improve vaccine antibody responses.[11,20,21] In a placebo-controlled poliovirus vaccination study, patients with a mild selenium deficit given 100 mcg selenium/day had better responses from T cells, virus challenge, and viral clearance.[23]

Typical adult therapeutic doses of selenium are around 150 mcg/day.[24]

Zinc
Zinc is important to innate and acquired immunity that supports natural killer (NK) cells and the maturation of T-cells, which are important in the response to infections and vaccines.[25,26] Low zinc in elderly populations is tied to increased susceptibility, longer illnesses, and increased mortality.[27] Supplementing 20 mg zinc/day in the elderly can restore activity to thymulin, a hormone that matures T cells.[28]

Typical adult therapeutic doses of zinc are between 25 and 40 mg per day.[29]

Vitamins A and D
Current evidence on vitamin A is equivocal in relation to improving vaccine response and depends on specifics of the population age, sex, vaccine being tested, and patients' baseline vitamin A levels.[30] While vitamin D plays an important immunomodulatory role, it does not appear to improve antibody production to influenza vaccines, even in elderly patients with vitamin D deficiency.[31,32] Adults receiving vitamin D supplementation before a booster dose of tetanus have higher antibody levels against tetanus.[13] In addition, several authors have recently shown that vitamin D levels are associated positively with better outcomes of COVID-19 infection in hospitalized patients, which suggests that it would be prudent to ensure that patients have adequate intake and levels of key vitamins like A and D.[33]

Typical adult therapeutic doses of vitamin A are around 10,000 IU and vitamin D between 1,000 and 10,000 IU daily.[34,35]

Probiotics and prebiotics

A 2018 systematic review found various strains of probiotics can increase efficacy for 17 different vaccines.[36] Probiotic administration may also increase the length of time a vaccine is effective.[36] A meta-analysis of randomized control trials (RCTs) found probiotics and prebiotics interventions between 2-28 weeks improved seroconversion and seroprotection of influenza vaccines.[37] Half of the studies used *Lactobaccilus* (*L. casei/L.paracasei* most common), with *Bifidobacterium* being the next most common.[37] For prebiotics the most commonly used were fructo-oligosaccharide and galacto-oligosaccharide.[37] Prebiotics and probiotics had the largest effects when given before vaccination, and the effects increased with length of time they were supplemented.[37] In the meta-analysis, on average probiotics supplementation lasted 7 weeks, and prebiotic supplementation lasted 16 weeks.[37] Another recent meta-analysis looking at 12 RCTS with 688 participants found that participants in the prebiotics/probiotics groups had significantly higher antibody titers after vaccination for influenza A & B, including vulnerable elderly populations in nursing homes.[38] Enhancing intestinal immune function through the use of probiotics appears to enhance the production of antigen-specific antibodies in response to vaccination.[39]

Given the diversity of probiotic strains that have been studied, a probiotic supplement with various species including Lactobacillus acidophilus*,* L. casei/ paracasei *or* L. rhamnosus, *and* Bifodobacterium lactis *may be a prudent option.*

Botanicals and mushrooms

Few botanicals have been studied in regard to specifically increasing vaccine effects and efficacy. A small study using a standardized extract of *Echinacea angustifolia* found a reduction in respiratory symptoms when the extract was taken for the period surrounding influenza vaccine and compared to vaccine or extract given alone.[40] This suggests there may be an additive or synergistic effect. A small randomized controlled study found a mushroom extract called active hexose correlated compound (AHCC) improved response to influenza B vaccine, with significant increases in antibody and key lymphocyte levels.[41] The supplement was given at a dosage of 3 g/day for 2 weeks immediately after vaccination.[41] Another small double-blind placebo controlled study found Maitake mushroom (AKA *Grifola frondosa*; hen of the woods) at a dosage of 6.825 g/day for 12 weeks (4 weeks before vaccination, 8 weeks after) significantly improved antibody levels in older adults and further reduced upper respiratory symptoms.[42]

Support for those who are medically contraindicated for vaccination

A COVID-19 vaccine will not be a "one-size-fits-all" therapy. Many people will either not be good candidates or choose not to get a vaccine for various reasons. At time of writing (December 2020), vaccine candidates have mostly been studied in adults, with the exception of the Pfizer/ BioNTech SE study, which gained FDA approval to enroll children as young as 12 in October 2020.

While the evidence presented in this document is related specifically to factors that may impact vaccine efficacy, providers will be aware that there is a much greater body of evidence to support the role for diet, lifestyle, and supplement interventions in enhancing natural immunity. Metagenics Institute has compiled clinically actionable resources related to COVID-19 and supporting immune health.

It's important to reiterate, **the interventions discussed in this piece and the resources linked to have not been studied in relation to COVID-19** but are intended rather to inform medical professionals to help their patients navigate this challenging and ever-changing landscape. Our hope is to help clinicians and their patients have meaningful, informed discussions to choose options that best fit the individual patient.

Further resources:*

FDA COVID-19 Vaccine Information Page

CDC Vaccine Testing and Approval Process Page

CDC COVID-19 Vaccination Resources

NY Times Coronavirus Vaccine Tracker

*Metagenics Institute has no affiliation with these organizations.

Citations:

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