**Possible Preventative Vaccination Strategy Against SARS-CoV-2 Via The Live Attenuated Measles-Mumps-Rubella (MMR) Vaccine**

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The broad range of severity in the SARS-CoV-2 (Coronavirus disease 2019 or COVID19) disease has been of high interest in order to combat the global pandemic. Recently, trained innate immunity (TII) has been a concept investigated in a possible alternate preventative Measles-Mumps-Rubella (MMR) vaccination strategy to strike against COVID-19, while a vaccine for the virus is being mass produced and administered worldwide. This strategy has been based off of previous investigations of determining conditions to induce innate mediated responses in polymicrobial infections. TII is the biological process of introducing a pathogen to induce a broad and non-specific innate immune response, that provides protection against subsequent infections. Previous work was utilized on studying a low-virulent fungal infection, that when subsequently challenged with a lethal fungal and bacterial polymicrobial infection causing sepsis, was met with an innate non-specific immune response. The few contraindications of the MMR vaccine, even for immunocompromised patients, could serve as a preventative measure to stall COVID-19 severity of high-risk individuals everywhere. This premise was applied to hypothesize a retrospective inverse correlation study of MMR Immunoglobulin G (IgG) titer levels and severity of COVID-19 from recovered patients. Indeed, a significant inverse correlation of MMR titers, specifically Mumps, and COVID-19 severity was found that may serve as a preventative strategy before mass COVID-19 vaccination.

**Introduction**

 There is a need for more aggressive interventions outside of masks and social distancing before herd-immunity as a result of widespread vaccination efforts is accomplished. While the production of the COVID-19 vaccine is underway and being administered, many people are still at high risk of infection (1). Researchers have noted that there are many disparities of COVID-19 symptoms and severity among many different age groups and nationalities (1). The results of COVID-19 tests from frontline health care workers, essential workers operating to maintain functions of everyday life and roommates exposed to individuals with COVID-19 experience a wide variety of results and symptoms (2). Even when infected, the results of individuals tested and disparities of symptoms are still unclear on who will experience what symptoms. The sequelae from COVID-19 that is associated with pulmonary inflammation and sepsis (a late and life-threatening condition when the immune system’s response to infection spreads throughout the body damaging organs and tissues) is often the most severe case where hospitalization and intubation is required (1). On the opposite, many individuals are routinely exposed mask-less and non-socially distanced to those tested positive and are asymptomatic and never indicate a positive test (1).

 Previous studies have theorized that the live attenuated MMR vaccine provides nonspecific effects on COVID-19 and other unrelated illnesses (1, 2). The trained innate immunity might be the cause of these non-specific responses. This claim into how the innate immune system can provide protection is derived from animals and plants that lack an adaptive immune system that still possess protection from subsequent infections (3). Recent studies have investigated the conditions and scope of this protection from TII in primary challenges (inoculation to observe whether an effect is elicited) of Candida species and subsequent Candida/Staphylococcal polymicrobial infections which would otherwise cause the life-threatening condition of sepsis (3, 4). Interestingly, if low-virulent challenges are followed by lethal polymicrobial infections (i.e. the same *Candida* species and a *Staphylococcus aureus* infection), then protection and even cross-protection to other infecting species has resulted (4). This protection has thought to have been from not the adaptive immune response, rather a “trained tolerogenic immunity” particularly from myeloid-derived suppressor cells (MDSCs) that are derived from the common myeloid progenitor cell (3). Murine models that were deficient in T and B cell production that were still protected from subsequent infections supports this claim of the trained immunity (3). Furthermore, mice depleted of macrophages still produced a protective response. The characterization of (MDSCs) is associated to provide this nonspecific response and reduction of the cytokine (chemicals produced by immune cells that affect other cells) storm against sepsis (3). The authors noted that to support this claim and investigate further, they presented the case of the U.S.S. Roosevelt which had 955 sailors test positive for COVID-19, but only one sailor required hospitalization (2). The authors deduced this is likely attributed to all U.S. Navy recruits receiving the MMR vaccination at basic training (2). This novel claim, along with previous studies on the TII to induce broad non-specific protection, has served as the hypothesis to investigate MMR IgG titer levels and the severity of COVID-19 from recovered patients.

**Recent Progress**

 The analysis of MMR titers of recovered COVID-19 patients aimed to answer a preliminary question: do any of the MMR titer levels relate to COVID-19 severity? To determine the correlation, this study had two groups, where the first group all had some form of the MMR vaccine and were born after 1 December, 1976 with fifty participants. The second group had thirty subjects all born before 1 December, 1976 to serve as a comparison group as the only reliable way to separate those that did not receive the MMR vaccine but like acquired antibodies from natural infection. Participants were required to have tested positive for COVID-19 and fill out an assessment of severity of the disease symptoms. Based off the participant’s disease symptoms, a point was given for a specific symptom indicated. The points were split across five levels of severity from “functionally immune” at 0, “asymptomatic” at 1, “mild” from 2-10, “moderate” from 11-20, and “severe” from 21-30 (1).

 Results from the study showed that specifically the mumps titer levels had a significant inverse correctional effect (R2 = -0.71, P<0.001, α=0.05) indicating a strong support of the hypothesis, as well as a significant inverse correlation between mumps titer levels and symptom score (R2 = -0.58, P<0.001, α=0.05) (1). Along with a possible correlation, the researchers determined a mean mumps titer levels of arbitrary units per milliliter (AU/mL) for the severity of COVID-19. 134-300 AU/mL corresponded to those asymptomatic and functionally immune, those below 134 AU/mL corresponded to the mild category, those with less than 75 AU/mL corresponded to the moderate category, and the most severe category all had less than 32 AU/mL of Mumps titer levels. Interestingly, the probable correlations were not age dependent across the experimental and comparison group. Even with a significant probable correlation, the exact molecular mechanism of the TII response is unknown. The results of this retrospective correlation study has allowed the initiation of more studies into alternative live-attenuated vaccine investigations for at-risk populations and investigating the role of the TII (1). Currently, there are studies in progress to determine how the molecular mechanisms of the TII response works from the MDSCs that inhibits sepsis, one of the late and life-threatening symptoms from COVID-19 (1).

**Discussion**

 Researchers had to acknowledge that only a selection of antibodies could potentially cross-protect against COVID-19, which ranged from a variety of sources. Antibodies could source from the common MMR II vaccine, a different monovalent MMR vaccine (containing one strain only), older MMR vaccines with different strain compositions, and natural antibodies from infection most commonly for those born before 1957 (1). The critical finding of the study was the significant inverse correlation between mumps titer levels, rather than measles or rubella titer levels, and the severity of COVID-19, independent of age. The relation of the mumps titers was compared to the Measles or Rubella titers was not known and provides more unknowns for further study in to mump antibodies and COVID-19.

 Due to the nonrandom selection process of the study in both study groups, it is difficult to tell where participants acquired the antibodies that could be interacting with COVID-19 in the immune response. Further studies with experimental and control (rather than comparison group as this study was conducted) was recommended by the authors to definitively investigate the correlation. While the comparison group had a lack of correlation for mumps titer levels and severity, the broad range of antibody origin outside of MMR antibodies could be possible for the lack of correlation (1). It is also unknown why some participants retained high mumps titer levels longer than others. Initial vaccination as a child, vaccine indications for child-bearing age women for transplacental immunity, and booster series due to various reasons may be attributed to the retained titer levels over time (1). From CDC data, the authors claim that due to the indication for children to receive the MMR vaccine, mumps titer levels start to decline after age 14. With this claim, and associating low COVID-19 cases between the ages of 12 months to 21 years of age (peaking at 2.17%) is thought to be mostly likely from MMR-induced immunity (1). Indeed, the authors referenced CDC data that there were 65% more COVID-19 cases for infants less than 12 months, since MMR vaccination is indicated for infants 12-15 months old (1).

 The significant inverse correlation is not a direct causation; however, the results support previous studies in the TII where an initial challenge of a live-attenuated vaccine can induce epigenetic reprogramming of innate immune cells for subsequent non-related infections; however, the exact molecular mechanism for how a live attenuated vaccine induces a TII response is still under investigation. The authors claim that the MMR induced TII response might be from the MDSCs that improves the COVID-19 symptoms, same response from the polymicrobial infection studies (1). COVID-19 is able to evade early immune responses and exacerbate late immune responses that attributes to the severe cytokine storm associated with severe acute respiratory distress syndromes (1). Previous studies have discussed that the relative age of the MDSCs compared to each other, have a role in downregulating cytokine storms before sepsis can occur (4).

 The importance of this study’s results warrants more investigation into the mumps antibody interactions with COVID-19, a randomized clinical trial of MMR vaccination with a larger sample size, and to determine a causal link between MMR immunity and COVID-19 severity, as well as characterizing the molecular mechanisms of MDSCs and their role in the TII response. If these studies further support MMR immunity and dampening the symptoms and severity of COVID-19, an alternate preventative MMR vaccine strategy can be utilized to protect and dampen severity of at-risk populations before receiving the COVID-19 vaccine.

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