Use of a Live Attenuated Vaccine as an Immune-based Preventive Against COVID-19-associated Sepsis

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Study Protocol

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Protocol Title: Use of a Live Attenuated Vaccine Repurposed as an Innate Immune- Based Preventive Against COVID-19- Associated Sepsis/Inflammation

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Project Description

The objective of this randomized clinical trial is to test whether administration of live attenuated MMR vaccine (measles mumps rubella; Merck) to eligible adults at risk for contracting COVID-19 , can induce non-specific trained innate immune leukocytes that can prevent/dampen pathological inflammation and sepsis associated with COVID-19 infection, if exposed. Mechanistically, we will monitor whether MMR (booster) vaccination induces non-specific immune leukocytes that limit pathological inflammation and sepsis, a critical sequelae associated with COVID-19 infection. The use of live attenuated vaccines (LAV) has been shown to provide beneficial non-specific effects, including reduced mortality and hospitalization due to unrelated infections (1-3). These non-specific effects are a result of inducing "trained innate immunity" via leukocyte precursors in the bone marrow to function more effectively against broader infectious insults (4,5). Work from our laboratory demonstrated that vaccination with a live attenuated fungal strain induces "trained innate" protection against lethal polymicrobial sepsis by myeloid-derived suppressor cells (MDSCs) (5-7). Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis (8). According to CDC guidelines, vaccination with MMR in immunocompetent individuals has no contraindications and may be especially effective for healthcare workers and first responders who can easily be exposed to any number of infections. While other current clinical trials have been initiated with the live attenuated BCG vaccine for the purpose of inducing cells trained for non-specific immune enhancement against COVID-19,(https://www.sciencemag.org/news/2020/03/can-century-old-tb-vaccine-steel-immune-system-against-new-coronavirus; https://www.nytimes.com/2020/05/01/opinion/sunday/coronavirus-vaccine-innate-immunity.html), we herein propose a randomized control clinical trial with live attenuated MMR vaccine (repurposed) to induce trained non-specific MDSCs as a preventive measure to inhibit the severe lung inflammation/sepsis associated with COVID-19 infection. Our overarching hypothesis is that administration of the live attenuated vaccine in adults will induce the trained innate MDSCs that can serve as an immune-based preventive against the severe sequelae of COVID-19 infection. Accordingly, this trial has potential for high impact as a "low risk-high reward" response to the COVID-19 pandemic as we have recently reported (9).

Experimental Design

Clinical Design.

Eligible healthcare workers (HCW), first responders, and non-healthcare individuals in the greater New Orleans area (n=60) meeting eligibility criteria will be enrolled into a 12 month study conducted by the Louisiana State University Health Sciences Center Clinical & Translational Research Center (LSUHSC CTRC) clinical staff affiliated with the Louisiana Clinical and Translational Research Science (LA CaTS) Center and blindly randomized to receive the live attenuated M-M-R® II vaccine or placebo (sterile

saline) via subcutaneous injection in the arm at a baseline visit following informed consent. Subjects will be recruited from the LSUHSC, LSU Dental School, local hospitals, long-term care facilities, EMS stations, and the general community throughout the greater New Orleans area by distributing recruitment flyers, social media postings, and by designated on-site recruitment activities conducted by study personnel within local facilities. The flyers and social media postings will have contact information for individuals to call for more information or to schedule an appointment. Additionally, subjects may be referred to the study by other participants or individuals aware of study activities. Subject consenting, interviewing, vaccine administration and biospecimen collection will be performed by the CTRC staff, under full Personal Protective Equipment (PPE) protection. Following informed consent, subjects will be asked to complete the Baseline Demographic & History Questionnaire disclosing their demographic information, employment, medication, vaccination, and medical history. Specifically, the medical history will place emphasis on the presence of diabetes, hypertension, heart disease, and their treatments/medications. Subjects will then have their height, weight, body mass index (BMI), vital signs, and pulse oximetry measured. Female subjects of childbearing potential will be given a urine-based pregnancy test. Approximately 30cc of blood will be collected along with a nasopharyngeal swab for baseline laboratory analyses (serology, RNA, flow cytometry). When available, a finger prick blood sample will be obtained in addition to the other biospecimens for SARS-CoV-2 antibody testing. SARS-CoV-2 antibody testing will occur at the baseline visit, optional 12 month visit, and upon a positive COVID-19 result by nasopharyngeal swab collected in the CTRC (at the subject's availability).Those subjects that satisfy the inclusion and exclusion criteria (Eligibility Criteria) will be blindly randomized to receive the live attenuated M-M-R ® II vaccine or placebo (sterile saline) via subcutaneous injection. Repeat biosampling will occur on days 14 (+/- 2 days), 30 (+/- 2 days), 60 (+/- 4 days), and at an optional 12 months (+/- 7 days) post-vaccination. At each follow-up visit, anthropometric measurements, vital signs measurement, and symptom assessment for the presence of symptoms related to COVID-19 infection (fever, headache, myalgia, cough, loss of taste or smell, breathing problems), general well-being (i.e., pain, dental concerns, sleep patterns, general stress level, fatigue), and any changes in medications, medical status, and employment will be collected utilizing the Follow-up Symptom & History Questionnaire. Telephone follow-up calls utilizing the Follow-up Symptom Assessment & History Questionnaire will be made on a monthly basis between the 60 day follow-up and the optional 12 month endpoint visit at designated timepoints. Subjects will additionally be asked to come into the clinic at their convenience for a mid-point study visit and follow-up biospecimen collection (blood only). Subjects will have the option to schedule this mid-point visit at 6, 7, or 8 months after enrolling into the study. Subjects will have the option to schedule a 12 month follow-up visit where anthropometric measurements will be taken, vital signs measured, a symptom assessment for the presence of symptoms related to COVID-19 infection taken, and a fingerprick for blood sampling to assess the presence of SARS-CoV-2 antibodies will be administered when available. Should a subject develop symptoms potentially associated with COVID-19 infection at any point during the 12-month study period, he/she will be seen in the clinic by the Infectious Disease (ID) Co-investigator

and a repeat collection of blood and nasopharyngeal biospecimens will be performed for analysis, and the subject will be asked to complete the Follow-up Symptom & History Questionnaire. Subjects will be asked to report the development of any potential COVID-19 infection related symptoms or positive COVID-19 infection testing outside of the study, as well as any symptoms potentially related to MMR vaccination. Should a subject become admitted to the hospital related to COVID-19 infection, in-patient information will be obtained via the electronic medical record (EMR) when available.

Subjects will also be enrolled and followed at additional local facilities within the greater New Orleans area. If enrolled at a local facility other than the LSUHSC CTRC, subjects will have their baseline visit conducted on-site at the enrolling facility. Should work schedules prohibit follow-up visits from being performed at the LSUHSC CTRC, subjects will have the option to have them conducted at the enrolling collaborating site. When possible, follow-up visits will be completed at the LSUHSC CTRC. The same biospecimens and study procedures will be collected and followed at all collaborating sites for all study visits.

Subjects will be compensated $25.00 for each clinic study visit

Eligibility Criteria

Inclusion Criteria:

- 18-85 years of age
- Able to provide a signed and dated informed consent
- Able to provide pre-randomized blood specimen

Exclusion Criteria:

- Any known MMR vaccine contraindication
- Fever
- Weakened resistance toward infections due to a disease in/of the immune system
- Individuals receiving medical treatment that affects the immune response or other immunosuppressive therapy in the last year (see excluded medications)
- Individuals with a congenital cellular immunodeficiency
- Individuals with a malignancy involving bone marrow or lymphoid systems
- Individuals with any serious underlying illness (such as malignancy). ***People with cardiovascular disease, hypertension, diabetes, and/or chronic respiratory disease are eligible if not immunocompromised (at the discretion of the ID Co-investigator)***
- Individuals with known or suspected HIV infection, even if asymptomatic or has normal immune function (Due to the risk of disseminated MMR infection)
- Individuals with an active skin disease such as eczema, dermatitis or psoriasis at or near the site of vaccination. ***A different site can be chosen if necessary***
- Pregnant or women who think they may test positive for pregnancy in the next month following MMR vaccine administration

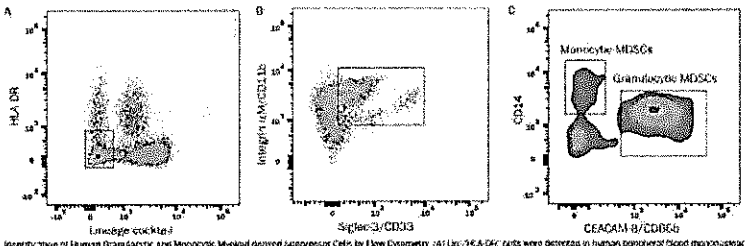
- Individuals who have received a MMR or another live vaccine (i.e., Zostavax, nasal spray flu vaccine) within the last year
- Individuals requiring another live vaccine to be administered within the month following study enrollment/randomization
- Individuals with known anaphylactic reaction to any of the ingredients present in the MMR vaccine

Primary outcome measures will be peripheral blood monocytic MDSCs (M-MDSC) and/or granulocytic MDSCs (G-MDSC) determined by flow cytometry from whole blood samples. Specifically, documented increases in the MDSCs per subject from baseline through 30-60 days post-vaccination is expected in the MMR group compared to placebo group. Measles antibodies are also expected to increase in the MMR group and will serve as a control for the MMR vaccination. Stationary levels of MDSCs and measles antibodies are expected in the MMR group over the 12-month period. We will perform the COVID-19 RNA testing at baseline, 14, 30, and 60 days post-vaccination, and at any point over the 12-month period that symptoms arise. All patients that are COVID-19+ at baseline or become COVID-19+ through the study will be included for secondary outcome analyses. The Secondary outcome measures will be COVID-19 antibodies (seropositive) as evidence of infection, sepsis/lung inflammation, ICU/ventilator usage, in-patient health related co-morbidities and self-reporting mental status (such as general fatigue/stress level) over the 12-month period post-vaccination. In-patient information will be obtained through the EMR when available. Out-patient information will be obtained via self-reporting utilizing the Follow-up Symptom & History Questionnaire.

Laboratory Design

Blood samples will be used for leukocyte analyses, and presence of SARS-CoV-2 and measles, mumps, and rubella antibodies. Nasopharyngeal sampling will be used to detect the presence SARS-CoV-2 RNA. Urine will be used for the pregnancy test. *Peripheral MDSC Analysis*: Whole blood samples will be shipped to a commercial fee-per-sample flow cytometry testing facility (Flow Contract Site Laboratory, Bothell, WA) and analyzed for M-MDSCs ($CD33^{high}CD14^{high}HLA\text{-}DR^{dim}$) and G-MDSC ($CD33^{high}CD66b^{high}HLA\text{-}DR^{dim}$) populations (see figure). For the MMR group samples will be evaluated at baseline, 14, 30, and 60 days post-vaccination. For the placebo group, although blood will be drawn at the same times, only the baseline, 30-day, and 12-month samples will be evaluated for MDSCs.

Analysis of Human Granulocytic and Monocytic MDSCs by Flow Cytometry



Identification of Human Granulocytic and Monocytic Myeloid-derived Suppressor Cells by Flow Cytometry. (A) Lin-/HLA-DR- cells were detected in human peripheral blood mononuclear cells by staining with a Lineage cocktail containing Alexa Fluor 700-conjugated Mouse Anti-Human CD3e and CD19 Monoclonal Antibodies (R&D Systems, Catalog # FAB100N and # FAB4807N, respectively) and an Alexa Fluor 700-conjugated Mouse Anti-Human HLA-DR Monoclonal Antibody (R&D Systems, Catalog # FAB4868P). Lin-/HLA-DR- cells were gated. (B) CD11b+/CD33+ cells were detected in the Lin-/HLA-DR- cell population by staining with an APC-conjugated Mouse Anti-Human Siglec-3/CD33 Monoclonal Antibody (R&D Systems, Catalog # FAB1137A) and an Alexa Fluor 405-conjugated Mouse Anti-Human Integrin αM/CD11b Monoclonal Antibody (R&D Systems, Catalog # FAB16981V). CD11b+/CD33+ cells were gated. (C) Human granulocytic myeloid-derived suppressor cells (Lin-/CD11b+/CD14-/CD33+/CEACAM-8+/HLA-DR-) and monocytic myeloid-derived suppressor cells (Lin-/CD11b+/CD14+/CD33+/CEACAM-8-/HLA-DR-) were detected in the Lin-/HLA-DR-/CD11b+/CD33+ cell population by staining with a PE-conjugated Mouse Anti-Human CEACAM-8/CD66b Monoclonal Antibody (R&D Systems, Catalog # FAB4868P) and a PerCP-conjugated Mouse Anti-Human CD14 Monoclonal Antibody (R&D Systems, Catalog # FAB3832P).

M/M/R Virus Serological Analysis: Blood serum will be analyzed for measles, mumps, and rubella virus IgG in the PI laboratory by ELISA (MyBioSource; San Diego, CA) at baseline. The measles antibody titers will be measured at all follow-up visits as a positive control for vaccine efficacy. *COVID-19 PCR Detection:* Nasal swabs wills be tested for SARS-CoV-2 RNA by our co-investigator Dr. Cameron using RT-qPCR Rapid Detection Kit (MyBioSource; San Diego, CA). *COVID-19 Serological Analysis:* Finger prick blood sample will be obtained and tested for the presence of antibodies against SARS-CoV-2 IgG on site in the CTRC by laminar flow test kit (Ray Biotech). If the laminar flow kits are not available in high enough quantities the serology will be conducted in the PI lab by 2019-nCoV/Coronavirus ELISA using the serum (MyBioSource; San Diego, CA). All serum samples will be stored. For those individuals that test positive for COVID-19, IgG antibodies to measles, mumps, and rubella viruses (MyBioSource) will be monitored (in the PI laboratory) and used for correlates to health status. This will include MMR and placebo subjects. Should other correlates for immune mediators be of interest to evaluate (parameters tested in other clinical trials, i.e., BCG trials) the stored specimens can be used for analyses.

Power analysis – sample size

The sample size justification is based on the primary outcome of the 30-day fold change of MDSCs. Based upon published reports (10), the means of MDSCs (CD33+HLA-DR-) and the CD11b+CD15+ MDSC subset were 0.22 and 0.11 with a standard deviation of 0.03 for healthy adults using the two-sided t-test. The power is set to be 80% and the significant level is 0.05. With a total of 50 participants (25 per study group), the minimum detectable 30-day fold changes of MDSCs for the MMR group are expected to be 1.12 and 1.24. This is under the assumption the 30-day fold change in the MMR group will be 5-10 compared to 1 in the placebo group. Furthermore, we estimate 10% prevalence of COVID-19+ in the participants during the 12-month follow-up period. A total of 50 subjects will achieve sufficient power for the primary outcome (MDSCs), and provide preliminary data for COVID-19+ cases relative to the secondary outcomes of longitudinal health measures. While loss to follow-up with HCW and first responders is expected to be minimal we will enroll 60 to account for a potential 20% loss to follow-up.

Data analysis

Eligible subjects (n=60) will be randomized by the LSUHSC CTRC staff using block randomization via the online Research Randomizer version 4.0 computer software. This is a free service offered by the Social Psychology Network for researchers, students, and others interested in generating sets of random numbers. The program is best described as a "pseudo-random number generator" because numbers are generated by use of randomness. Research Randomizer uses the "Math.random" method within the Java Script programming language as the core method for generating its random numbers, http://www.randomizer.org .

The participant's demographic, MDSCs, and COVID-19 related clinical characteristics will be summarized using descriptive statistics by the two study groups (placebo and MMR) at each time-point. For the primary outcomes, the MDSC levels between the placebo and the MMR groups at each time-point will be compared using the t-test if the original or transformed data are normally distributed. The changes of MDSCs between baseline and time points post-vaccination for the two study groups will be summarized using fold-change, and the difference of the MDSCs' changes between the groups will also be tested using the paired t-test. For the MMR group, the changes of antibodies to the measles virus between a specific time-point and baseline will be tested using the paired t-test. We are also interested in evaluating the MMR vaccine impact on MDSCs over time. The linear mixed model with the MDSCs as the outcome will be used for testing all available repeated measures. The subjects are considered random, and all predictors are considered as fixed effects. Both univariate and multivariable models adjusting for other factors (such as age and gender) will be performed. Only those testing positive for COVID-19 will be included for analyses related to secondary outcomes. Accordingly, at the end of the study, the categorical secondary outcomes (such as COVID-19 co-morbidities, especially those related to sepsis/lung inflammation, ICU/ventilator usage) between the MMR and placebo study groups will be compared using the Fisher's exact test. For comparisons of continuous outcomes (i.e., general fatigue/stress) between the two groups, the t-test will be applied.

Expected Results

Based on the inclusion/exclusion criteria, we expect that the vast majority of individuals given the MMR vaccine will show an increase in both granulocytic and monocytic MDSCs beginning at 14 days and increased further by 30 days. We expect a plateau at 60 days. We also expect increased titers of measles virus as an efficacy control by 14-30 days. We expect a low percentage of enrollees to be COVID-19 positive based on RNA testing at baseline (undocumented and unsuspecting), but we expect more positive cases in enrolled subjects during the 12-month follow-up period due to continued exposure to and community transmission of COVID-19. It is possible, that several enrollees may have been previously COVID-19 positive that will be confirmed by seropositive for COVID-19 at baseline. These will be subjects who may have had some health-related symptoms in the past months. The COVID-19 antibody+ group at baseline will be stratified separately in the analysis during the 12-month follow-up. We expect those who become COVID-19 positive in the MMR group to show symptoms of infection, but with reduced incidence of severe complications. Others may be completely asymptomatic altogether based on recent clinical observations. Health status may also be related to measles, mumps, and rubella antibody titers based on some potential evidence for cross-reactivity to COVID-19 epitopes (11), https://doi.org/10.1101/2020.04.10.20053207. While we focus on the 50-60 subjects to show differences in MDSCs as the primary outcome, together with the power to test COVID-19+ subjects for secondary outcomes, we would increase the trial to 400-500 subjects with increased funding that would likely result in 50+ COVID-19+ patients to follow over the 12-month follow-up period.

Risks

While there may be psychological, social, legal, and economic risks associated with COVID-19 infection, it is not expected that participation in the proposed project is associated with any of these risks, both within the MMR and placebo groups. The major risks associated with study participation are related to the MMR vaccine. There are few contraindications. The most frequently observed side effects are associated with the MMR vaccine are mild and include dizziness, visual changes, hypotension, and fainting, soreness or rash at the injection site, a generalized body rash, fever, and swelling in the glands of the cheek or neck. More serious reactions associated with the vaccine are rarely seen and include a life threatening allergic reaction, seizures which are often associated with fever, temporary pain and stiffness in the joints, pneumonia, swelling of the brain and/or spinal cord covering, and temporary low platelet count which can cause unusual bleeding or bruising. Additionally, people with serious immune system problems can develop a life threatening infection. The risks associated with phlebotomy include pain or bruising at the needle site, dizziness, and syncope. The risks associated with nasopharyngeal swabbing can include gagging and pressure or discomfort upon swab insertion and a small amount of bleeding after the procedure.

Facilities and Equipment

The PI/ Co-investigators have expertise in all areas surrounding this project. The CTRC is a fully functioning clinical trials unit affiliated with LA CaTs, an NIH funded statewide clinical research initiative since 2014. The PI is on the Executive Steering committee and several Key Components Areas, KCAs (Core) (Clinical Research Resources and Regulatory and Ethics). Our consultant (Shellito) is Director of Clinical Research Resources KCA. Our statistician is in the Biostatistics KCA and in the LSU School of Public Health.

Key Data

The objective of this randomized clinical trial is to test whether administration of live attenuated MMR vaccine (measles mumps rubella; Merck) to eligible adults can induce non-specific trained innate immune leukocytes that can prevent/dampen pathological inflammation and sepsis associated with COVID-19, if exposed. Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis. There is mounting evidence that the use of live attenuated vaccines (LAV) commonly administered during childhood, also provide beneficial non-specific immune effects, including reduced mortality and hospitalization due to unrelated infections. It has been proposed that LAV non-specific effects are a result of inducing 'trained innate immunity', which occurs when LAV "train" leukocyte precursors in the bone marrow to function more effectively against broader infectious insults. In support of this, work from our laboratory demonstrated that vaccination with a live attenuated fungal strain induces 'trained innate' protection against lethal polymicrobial sepsis (see figure).

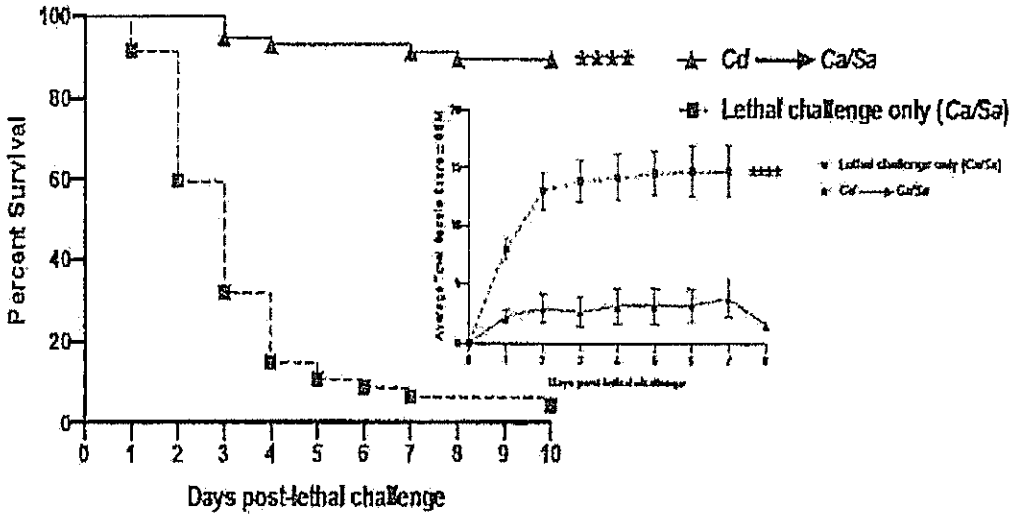


Figure 1. Protection against a lethal polymicrobial-mediated sepsis by vaccinationwith an avirulent yeast strain. Mice were vaccinated with avirulent (live attenuated)*Candida dubliniensis* (*Cd*) intraperitoneally followed by a lethal challenge with*Candida albicans and Staphylococcus aureus* (*Ca/Sa*) intraperitoneally 14 dayslater. Survival data are shown for 8 independent experiments with groups of 10 mice/ea. Inset shows sepsis scoring during the observation period after lethalchallenge. ****p<0.0001.

The protection is mediated by long-lived myeloid-derived suppressor cells (MDSCs) reported to inhibit septic inflammation and mortality in several experimental models. The general concept that the trained innate immunity induced by LAV can limit pathological inflammation is novel but not without precedent. There are several recently initiated clinical trials in Europe and Australia using BCG (live attenuated tuberculosis vaccine) in healthcare workers (HCW) to investigate trained innate 'enhancing' immunity against COVID-19. We herein propose a similar type of clinical trial with live attenuated MMR (repurposed) in HCW and first responders, but based on our work, we propose the induction of trained innate 'tolerogenic' immunity via MDSCs that can limit the severe inflammation/sepsis associated with COVID-19. The proposed clinical trial would take place in New Orleans, LA, an epicenter for COVID-19 infections and deaths. According to the CDC, there are few contraindications for adults to receive a live attenuated vaccine such as MMR if the recipient is immunocompetent, not pregnant, nor has previous allergies to vaccination. In fact, the CDC recommends MMR vaccination for high risk adults (i.e., healthcare workers) and people born before 1957 who did not receive the vaccine as a child.

One of the more interesting observations in comparing other viral respiratory coronavirus epidemics (SARS; MERS) vs. pandemics of seasonal influenza is the drastic difference in mortality rates in children compared to adults. Children are highly susceptible to seasonal flu, and mortality is in large part the result of secondary infections, including bacterial pneumonia and exacerbation of underlying chronic conditions. However, very few children were affected during the SARS (2003) or MERS (2012) coronavirus outbreaks and now as well for COVID-19, which are all associated with severe pulmonary inflammation and sepsis induced by the virus, and eventual organ failure. We reason that children are protected against viral infections that induce sepsis because of more recent

and frequent exposure to LAV (MMR, smallpox, chickenpox, BCG), that can also induce the trained suppressive MDSCs that limit inflammation and sepsis. Our overarching hypothesis is that administration of the live attenuated MMR vaccine in adults will induce the trained innate immune MDSCs that can inhibit the severe lung inflammation/sepsis associated with COVID-19 infection. As such, this trial may serve as a 'low risk – high reward' immune-preventive against the worst sequelae of COVID-19 infection.

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