

Could live attenuated MMR vaccine booster protect against the worst of COVID-19?

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Abstract (word count – 149)

We strongly encourage MMR vaccination as a preventive measure against the worst sequelae of COVID-19. There is mounting evidence that live attenuated vaccines, including MMR, provides protection against lethal infections unrelated to measles, mumps, or rubella. Aside from adaptive immunity, it has been postulated that live attenuated vaccines also induce ‘trained’ non-specific innate immunity for improved antimicrobial function. Work from our laboratory demonstrated that vaccination with a live attenuated fungal strain induces trained innate protection against lethal polymicrobial sepsis. The protection is mediated by myeloid-derived suppressor cells (MDSCs) reported to inhibit sepsis and mortality in several experimental models. Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis. Vaccination with MMR in immunocompetent individuals has no contraindications and may be especially effective for healthcare workers. This concept of live attenuated vaccination to fight the COVID-19 pandemic can be ‘high risk high reward’ in saving lives.

Editorial

There is mounting evidence that the use of live attenuated vaccines, including MMR, provides secondary protection against lethal infections unrelated to measles, mumps, or rubella (1). Aside from inducing adaptive immunity, it has been postulated that live attenuated vaccines can also induce non-specific trained innate immunity by reprogramming or “training” leukocytes for improved antimicrobial function against subsequent infections (2). Work from our laboratory demonstrated that vaccination with a live attenuated fungal strain induces trained innate protection against lethal polymicrobial sepsis by limiting inflammation (3-5). In this model, the trained innate cells are myeloid-derived suppressor cells (MDSCs) that have been reported to inhibit sepsis and mortality in several experimental models (6-9). Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis (10), therefore we reason that the use of a live attenuated vaccine in immunocompetent adults may induce trained leukocytes that similarly limit inflammation/sepsis (i.e. an “innate booster”) associated with COVID-19.

One of the more interesting observations looking historically at other viral respiratory epidemics and pandemics of seasonal flu (influenza A virus), SARS, MERS, is the drastic difference in mortality rates in children compared to adults (11). Children are highly susceptible to flu; the CDC estimates that since 2010, flu-related hospitalizations among children younger than 5 years old have ranged from 7,000 to 26,000 in the United States with approximately 600 deaths in the past five years (12). However, very few children were affected during the SARS (2003) or MERS (2012) coronavirus outbreaks (11) and now as well for COVID-19 (<https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/children-faq.html>). This is likely due to differences in progression, pathogenesis, and cause of mortality between influenza and coronavirus infections. While mortality in flu is attributed to other co-morbidities such as bacterial

pneumonia (12), SARS and MERS is associated with severe pulmonary inflammation, sepsis, and high SOFA (sequential organ failure assessment) score, leading to acute mortality (10). We reason that children are protected against viral infections that induce sepsis because of more recent and frequent exposure to live attenuated vaccines (MMR, rotovirus, smallpox, chickenpox, BCG), which induce suppressive MDSCs that limit inflammation and sepsis.

The broader concept is that a live attenuated vaccine booster might be protective against the sepsis that can occur with COVID-19. In direct support of this concept, our recent work on trained innate immunity using an experimental murine model demonstrates that a primary challenge with live *Candida dubliniensis*, which is avirulent in mice, protects against lethal fungal/bacterial (*C. albicans*/*S. aureus*) sepsis of intra-abdominal origin or lethal intravenous (iv) challenge with *C. albicans* (3, 4). The protection is mediated by Gr-1+ MDSCs (phenotypically similar to neutrophils) that are induced in the bone marrow (similar to what has been observed with BCG vaccination) within 7-14 days (likely sooner as *C. dubliniensis* is detected in the bone marrow as early 24 h post-challenge). The protection is profound; lethal challenged mice succumb in 2-4 days from a severe systemic sepsis, while protected mice show no signs of sepsis/morbidity and eventually clear the infection (3, 4). We hypothesize that MDSCs inhibit or control septic inflammation allowing innate immune antimicrobial defenses to clear the infection in the absence of lethal inflammation. This primary live yeast challenge is akin to a live attenuated vaccine. If our hypothesis is correct, the use of a live attenuated vaccine (i.e., MMR) may function similarly against COVID-19-associated sepsis. Older adults, while likely still possessing antibody titers from their childhood vaccines due to the presence of long-lived memory lymphocytes, will likely not have retained trained MDSCs, which have a more limited lifespan. Our mouse model shows the protective Gr-1+ MDSCs are relatively long-lived compared to normal innate Gr-1+ cells such as neutrophils. Protection is maintained between

60-120 days post vaccination (3, 4) which may translate to a longer time frame in humans.

Therefore a live attenuated vaccine booster for older adults may re-induce MDSCs that could provide protection against the most lethal sequelae of COVID-19 such as damaging lung inflammation and sepsis.

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 allergic responses to vaccination

[\[https://www.cdc.gov/vaccines/vpd/mmr/hcp/recommendations.html\]](https://www.cdc.gov/vaccines/vpd/mmr/hcp/recommendations.html). In fact, MMR vaccination is recommended in adults at high risk such as health care workers and people born before 1957 who did not receive the vaccine in childhood []. At the very least the MMR vaccine will provide a booster immunization against measles, mumps, and rubella for older adults, which may be otherwise recommended in areas with high rates of unvaccinated children.

The most urgent need for an innate booster vaccine is for healthcare workers who are in the trenches treating COVID-19 patients. There is some recent precedent for this strategy. A group in the Netherlands has initiated a clinical trial testing vaccination with BCG (live attenuated tuberculosis vaccine) or placebo in high risk healthcare workers for the purpose of inducing trained innate immunity [\[https://www.sciencemag.org/news/2020/03/can-century-old-tb-vaccine-steel-immune-system-against-new-coronavirus\]](https://www.sciencemag.org/news/2020/03/can-century-old-tb-vaccine-steel-immune-system-against-new-coronavirus). The lead group initiating the trial have suggested that the trained innate cells induced by BCG remain in humans for a period of roughly one year. Hence, if the vaccine is functionally protective, recipients should be protected through the acute crisis period of the current COVID-19 pandemic until other therapies or a conventional vaccine is available. While BCG is not used in the US (or the UK) for various reasons, we suggest that a very similar trial should be started here in the US with MMR. While

such a trial during this crisis time will not have all the components of a true multi-phase clinical trial, time is of the essence. In the end this could save lives and serve as a 'high risk – high reward' response to the COVID-19 pandemic.

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