Review 1: "Efficacy of the Measles-Mumps-Rubella (MMR) Vaccine in the Reducing the Severity of COVID-19: An Interim Analysis of a Randomised Controlled Clinical Trial"

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RR:C19 Evidence Scale rating by reviewer:

- Potentially informative. The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

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Review: Since the beginning of the pandemic, there has been intense debate about the use of live attenuated vaccines (non-specific vaccines) to induce mucosal immunity to prevent, ameliorate disease, or reduce mortality due to SARS-CoV-2 infections\(^1\)-\(^3\). Since then, there have been several clinical trials evaluating the use of various vaccines capable of inducing trained innate immunity to protect individuals from SARS-CoV-2 infections and complications of COVID-19, with varying results. However, this manuscript demonstrates a protective effect of this approach in reducing the severity of COVID-19. This is a highly impactful clinical finding that may have significant public health implications right now, but also for tackling future pandemics due to respiratory viruses.

Briefly, the clinical trial by Fedrizzi et al. randomized patients between 18 and 60 to receive MMR vaccine or placebo to prevent primary SARS-CoV-2 infections by serial monitoring of nasopharyngeal swabs by RT-PCR. While MMR vaccine did not prevent incident cases of SARS-CoV-2 infections, it was associated with a 48% reduction in symptomatic COVID-19. In addition with one dose of MMR vaccine. There was also a reduction in requirement of SARS-C-V-2-specific treatment in about three-fourth of infected patients after receiving MMR vaccine. This is encouraging news in many parts of the world still struggling to control emergence of the new “delta variant” with shortage of vaccine supply chains. MMR vaccine provides an interim solution to control infections in unvaccinated people and buys more time to provide specific vaccinations for these individuals. Also, non-specific vaccines such as MMR could have great implications in opening up schools, restaurants and entertainment events, and help the growth of national economies in places there is a vaccine shortage.
While the study demonstrated “disease-modulating” efficacy of MMR, there are some limitations of this study that need to be addressed. First, the study enrolled patients who tested PCR negative on entry into the trial, but never confirmed serostatus. This could likely influence incident infections and especially, the severity of subsequent infections. Second, some of the participants may have also received COVID-19 vaccines prior to enrollment, which is also likely to influence the disease severity as shown in clinical trials.

A major debate in the use of non-specific vaccines is regarding the mechanism of protection that is observed in this trial. Several previous papers have suggested a role of “trained innate immunity” as a key mechanism to abort or modulate disease due to SARS-CoV-2. It is critical to delineate this mechanism of protection since this approach will have major implications in preventing deaths due to current or future pandemics. It should be noted that approximately millions of deaths attributable to SARS-CoV-2 infections were reported prior to the introduction of vaccines specific to SARS-CoV-2. The collection of available samples to delineate the levels and nature of protective immunity is critical for major advancement of this field. This clinical trial shows protective effect even after the first dose of MMR, which also opens up the debate of the requirement of multiple doses and the duration of effect of non-specific vaccines against SARS-CoV-2 infections.

In summary, non-specific vaccines do have a role in our ability to control current and future pandemics. There are two major hurdles in expanding immunizations globally to prevent the spread of SARS-CoV-2. These include skepticism and safety concerns of about “new vaccines” and lack of availability of vaccines in many parts of the world. In order to control the pandemic, a global approach is required to immunize and curtail the spread of infections. In this regard, the current study allows us a vaccination strategy that has decades of safety proven in patients of all age. While, this may not change the minds of skeptics, it may provide assurance to those who are reluctant to take the newer SARS-CoV-2 vaccines. Finally, this vaccine did not offer protection against incident cases of SARS-CoV-2, which is what many experts expected to see with trained innate immunity. An alternate strategy using vaccines such as oral polio vaccine (OPV) may have an advantage. OPV is oral, with excellent safety profile of repeated administrations, availability in multiple strains, the ability to replicate in mucosal tissues and induce mucosal type-I interferon response, is inexpensive, and has a proven record of preventing incident infections. As we have struggled through this pandemic, it is reassuring that we have now clinical evidence of a time-tested, safe, effective strategy to curtail present and future pandemics due to respiratory viruses.
References:


