Synopsis: Impact of influenza and MMR vaccine on SARS-CoV-2 infection

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Background

Various observational studies have reported an association between influenza vaccination and lower rates of infection with SARS-Cov-2 and less COVID-19 disease severity have been reported in large epidemiological studies in US, Brazil and Italy (1-4). Observational studies from the Netherlands showed also strongly reduced COVID19 infection rates among influenza-vaccinated healthcare workers, with ORs of 0.61 and 0.49 for the first and second wave of COVID-19, respectively (ref.5 and unpublished data). In addition, in-vitro immunological analyses showed that the quadrivalent inactivated influenza vaccine can induce a trained immunity program against SARS-CoV-2 (5). In-vivo vaccination against influenza was also shown to induce improved interferon responses against SARS-CoV-2, with modulation of hyperinflammatory responses (*in preparation*). Trained immunity could be the underlying mechanism for the potential protective effect of influenza vaccine, a mechanism that has also been proven for BCG vaccination, MMR and OPV vaccination (6). Currently, various clinical trials are being conducted to study the impact of BCG, MMR and OPV vaccination on COVID-19, but prospective clinical data on influenza vaccination are lacking.

Although specific COVID-19 vaccines have been developed and are proven effective, there are important reasons for assessing in a controlled randomized trial the effect of influenza and MMR vaccine on COVID19:

- Specific COVID-19 vaccines are still not yet available for all segments of the population, and especially not for the majority of the population in developing countries
- The emergence of new SARS-CoV-2 variants, especially the P1 variant from Brazil, may very well be associated with reduced response to vaccines. An immunomodulatory protective vaccine that protects in an antigen-independent manner would be of great importance.
- It would also be conceptually important to know whether influenza vaccine can induce heterologous protection against another viral infection, in the context of future pandemics

Objective
To study the impact of influenza vaccination on SARS-CoV-2 infection

Study design
Double-blind, randomized, clinical trial with a 1:1:1 randomization to either placebo, MMR vaccination or influenza vaccination.

Outcome measures
Primary outcome measure:

- SARS-CoV-2 diagnosis

Secondary outcome measures:

- Severe COVID-19, according to WHO criteria
- Hospitalization for COVID-19
- Invasive ventilation for COVID-19

- Death due to COVID-19
- Other respiratory tract infections (RTIs)

Population
Depending on the setting, evidence is needed in all age groups.
Consideration: elderly are at highest risk for severe COVID-19, so evidence in this age group is very relevant. However, they may also be first priority population to receive the specific corona-vaccination, limiting follow-up time for a trial. In addition, influenza or MMR vaccine may lead to lower immune response in elderly than in young people.
It is therefore likely that a more rational choice would be to perform the trial in a young (20-60 years old) population.

Exclusion criteria:
- Documented prior COVID-19 diagnosis
- COVID-19 specific vaccination
- Contra-indication for MMR or influenza vaccine

Intervention
Placebo vaccination, MMR or influenza vaccination

Data collection
Baseline visit to collect baseline information (demographics, medical history, medication use, vaccination history), for randomization and vaccination.
Participants should be followed long enough to reach sufficient number of endpoints, see sample size calculation. Information on primary endpoints, respiratory illnesses and doctor visits can be obtained from regular patient follow-up, using telephone follow-up, mobile apps or email/paper diaries. In-hospital information to be collected from patient medical records. (Serious) adverse events should be monitored and reported.

Sample size
Based on previous observational studies, MMR or influenza vaccination is hypothesized to reduce SARS-CoV-2 infection rates by 50%, based on available literature and data from our group.

Based on the power analysis detailed below, the study will be performed in the following groups:
- 2000 placebo
- 2000 MMR vaccinated
- 2000 influenza vaccinated

	6 months FU, 10% loss to FU	**6 months FU, no loss to FU**	**9 months FU, so 50% higher cum. incidence**	**6 months FU, fixed design, no interim analyses; no loss to FU**
	Nr of events (sample size)	*Nr of events (sample size)*	*Nr of events (sample size)*	*Nr of events (sample size)*
Effect 50% reduction				
Cum incidence				
1% → 0.5%	94 (14204)	94 (13538)	93 (9168)	92 (13240)
2% → 1%	93 (7046)	93 (6718)	92 (4532)	91 (6569)
4% → 2%	92 (3468)	92 (3306)	90 (2212)	90 (3233)
6% → 3%	**90 (2276)**	**90 (2170)**	**88 (1440)**	**88 (2121)**

Assumptions:

- Various cumulative incidences: likely to be 6% in 6 months
- Effect of intervention 50% reduction of SARS-Cov-2 infection
- Two-sided alpha of 0.05 and aim for 90% power
- Recruitment time: 1 month
- Follow-up time 6 – 9 months
- 10% loss to follow-up (alternative no loss-to follow-up)

References

1. Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the influenza vaccine on COVID-19 infection rates and severity. Am J Infect Control. 2021.
2. Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer APS, Daubenberger C, et al. Inactivated trivalent influenza vaccination is associated with lower mortality among patients with COVID-19 in Brazil. BMJ Evid Based Med. 2020.
3. Marín-Hernández D, Schwartz RE, Nixon DF. Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy. J Med Virol. 2021;93(1):64-5.
4. Ragni P, Marino M, Formisano D, Bisaccia E, Scaltriti S, Bedeschi E, et al. Association between Exposure to Influenza Vaccination and COVID-19 Diagnosis and Outcomes. Vaccines (Basel). 2020;8(4).
5. Debisarun PA, Struycken P, Domínguez-Andrés J, Moorlag SJCFM, Taks E, Gössling KL, et al. The effect of influenza vaccination on trained immunity: impact on COVID-19. medRxiv. 2020:2020.10.14.20212498.
6. Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, Curtis N, van Crevel R, van de Veerdonk FL, et al. Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection. Cell. 2020;181(5):969-77.