Thirty-two COVID-19 cases preventively vaccinated with MMR: all mild course

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Abstract

We would like to report here on our clinical observations in 212 subjects, vaccinated in our Center since the start of the Coronavirus disease-2019 (COVID-19) pandemic, with the mumps-measles-rubeola (MMR) vaccine and of whom thirty-two have presented COVID-19, all with a remarkably mild course.In the light of the COVID-19 pandemic, observing the highly contagious and virulent nature of the virus, new to mankind and for which no actual treatment nor vaccination exists, we have been searching for methods to enhance innate immunity. Moreover, the pandemic started in our country just after a rise in measles cases had motivated the Ministry of Health to recommend measles re-vaccination. Aware of the existence of trained immunity we decided to apply this concept and from March 2020 onward recommend MMR vaccination, but with extra emphasis among family members of COVID-19 cases. In June 2020 the American Society for Microbiology (AMS) speculated in a press-release that "the MMR vaccine could serve as a preventive measure to dampen .... COVID-19 infection."

To the editor

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In a prospective observational trial we followed MMR vaccinated subjects searching for COVID-19 cases. All patients were vaccinated subcutaneously with 0.5mL of the MMR vaccine containing live-attenuated virus ([?]1,000 $CCID_{50}$ of measles, [?]5000 $CCID_{50}$ of mumps and [?]1000 $CCID_{50}$ of Rubella virus) and follow-up was given by (bi)monthly phone calls or contact via electronic media. COVID-19 infection was considered confirmed with a positive result of the SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR), the detection of SARS-CoV-2 specific antibodies or the combined presence of a direct contact with a confirmed case plus anosmia/ageusia plus at least two classic symptoms. Direct contact with a confirmed case, accompanied by classic symptoms, but without olfactory nor gustatory alterations were considered highly probable cases. We graded the clinical severity of COVID-19 on a simplified scale we considered more suitable in an out-patient setting, see table 1.

Among the 212 vaccinated subjects there are 22 confirmed and 10 (highly) probable COVID-19 cases, twelve of them with hypertension, diabetes, obesity, smoker or uncontrolled asthma as possible risk-factors. All had minor respiratory symptoms at most. As people are generally very reluctant to go to a laboratory or take a chest X-ray, we have installed close follow-up in probable positive cases with pulse oximetry and home peak-expiratory-flow (PEF) measurements; only one uncontrolled asthmatic had one day hypoxemia. All received general supportive measures and the policy toward fever was permissive, keeping paracetamol use to a minimum. Some received off-label high-dose ivermectin the first two days. None presented respiratory insufficiency to the degree of needing oxygen.

Table 1. Cases of COVID (confirmed or highly probable) within weeks of MMR vaccination, COVID severity compared with case fatality rates for Mexico per age-sex group and per co-morbidity.

Age, sex	**Co-morbidities**	**COVID confirmation**	**COVID confirma**
74y, F	HT, overweight	Confirmed RT-PCR (-), IgG (+)	1 week
61y, M	None	Highly probable	4 weeks
65y, F	DM, obese	Confirmed IgM and IgG (+)	No symptoms
59y, F	None, very nervous	Highly probable	3 weeks
53y, M	Obese	Confirmed	2-3 weeks
56y, F	Obese	Confirmed RT-PCR (+)	-2 days
45y, M	Obese	Confirmed IgM and IgG positive	-9 days[1)]
43y, M	HT, DM, morbidly obese, metabolic syndrome	Confirmed (symptoms)	3 weeks
48y, F	Obese	Highly probable	Same day
45y, F	Overweight, AR, mild persistent asthma	Confirmed IgG (+)	2-3 weeks
36y, M	Obesity, AR, GERD	Confirmed IgG (+)	-1 day
39y, F	Morbidly obese	Confirmed (symptoms)	3 weeks
34y, F	Obesity, mild asthma	Confirmed IgG (+)	-1 day
25y, F	Mild smoker, overweight	Confirmed IgG (+)	-1 day
53y, F	None	Confirmed RT-PCR (+), IgG (+)	-2 days
39y, M	None	Suspected case	3 weeks
44y, F	AR, moderate persistent asthma	Confirmed	9 days
40y, F	None	Highly probable	3 days
30y, F	None	Suspected case	3 weeks
30y, F	None	Confirmed (symptoms)	3 days
29y, M	None	RT-PCR (-) Result IgG pending	1 day
25y, M	None	Highly probable	3 days
26y, M	None	Confirmed case (RT-PCR +) IgG (-)	1 month
8y, F	None	Confirmed IgG (+)	2 weeks
14y, F	AR, mild persistent asthma	Highly probable	9 days
14y, F	None	Confirmed RT-PCR e IgG (+)	7 days
13y, M	Uncontrolled asthma and allergic rhinitis	Confirmed (symptoms)	-1 day
10y, M	None	Highly probable	1 day
10y, M	None	Confirmed case RT-PCR and IgG (+)	6 days
25y, F	None	Confirmed IgG (+)	2 days
27y, F	Epilepsy	Confirmed RT-PCR (-), IgG (+)	2 weeks
27y, F	None	Confirmed (symptoms)	1 day

0 = asymptomatic, only test-positive; 1 = minimal symptoms; 2 = bad flu symptoms, no respiratory involvement; 3 = bad flu symptoms, mild respiratory involvement (PEF<85% predicted or personal best),

no need for supplemental oxygen; 4 = need for supplemental oxygen; 5 = need for intubation; 6 = fatal.

* At 2200m above sea-level (Mexico city)

** as calculated from case fatality per 1000 confirmed cases for each age-sex category as tabulated for August 3th, 2020 on the official website of the Mexican government: https://coronavirus.gob.mx/datos/#DOView

*** in same website: mortality indexes calculated from case fatality por 1000 confirmed cases with one of these co-morbidities: hypertension, diabetes or obesity. X = no statistics for this co-morbidity (e.g. asthma).

[1)] Retrospectively the GI symptoms seem to have been of his COVID. 9 days after onset of GI symptoms he came in for his MMR and 18 days after onset GI symptoms he tested IgM and IgG positive (took the test as a close contact tested positive).

DM = diabetes mellitus; HT = hypertension; nl = normal; PB = personal best;

The concept of trained immunity based on a heterologous immune response with non-specific memory dates back about a decade ago and refers to the enhanced immune response to a certain pathogen, after being exposed (by vaccination or natural illness) to another non-related pathogen(1) and Matricardi analyzed this in the context of the COVID-pandemic.(2) The immune reaction after a subsequent exposure to a non-related pathogen is faster in onset and accompanied by an increased production of certain cytokines. As such, trained immunity by nature is non-specific and carried by cells from the innate branch of the immune system, especially monocytes and NK-cells. Thus, it seems the innate immune system also has a certain kind of memory, as this enhanced response to a second pathogen can still clearly be detected three months, and in a lesser degree up to twelve months later. Interestingly, heterologous T helper-cell (Th)1 and Th17 adaptive immune responses to non-related pathogens also remained intensely elevated, even one year later.(3)

At molecular level a rise in aerobic glycolysis, oxidative phosphorylation and glutamine metabolism have been described in monocytes, induced by exposure to BCG, β-1,3-(D)-glucan from *Candida albicans* or heat-killed bacteria, i.e., via pathways involving toll-like-receptors and the cytosolic NOD-receptors.(4-6) However, the prolonged effects on the innate immune response ('innate memory') seem to be caused by epigenetic reprogramming of monocytes, not only in the circulation, but also at the myeloid precursor level in the bone marrow: after the initial stimulus the deoxyribonucleic acid strings in certain specific loci, linked to inflammatory cytokines, stay semi-uncoiled, thus facilitating a rapid transcription upon a subsequent stimulus.(4) The first studies in humans showed an enhanced production of cytokines such as IL-1β, Tumor necrosis factor (TNF)-α and interferon-γ, when human monocytes were stimulated *ex-vivo* with a second pathogen, after subjects had undergone BCG vaccination. The effect was still detected up to at least three months later.(4) Also, BCG vaccination of volunteers, followed one month later by inoculation with the live-attenuated yellow fever virus, resulted in a reduced viral load and a rise in serum IL-1β.(7)

Several clinical trials are now ongoing with BCG vaccination of SARS-CoV-2 exposed health-care workers in an attempt to reduce the severity of an eventual infection. However, one of the effects described in the above experiments with BCG-trained-immunity was a rise in IL-6, which made us reluctant to use this method due to immune over-activation described in severe COVID-19 cases linked to high IL-6 levels.

Apart from probably having a better safety profile, there are three reasons that made us think we could apply the concept of trained immunity administering the MMR vaccine.

1. Hong described trained immunity in newborn infants of HBV-infected mothers, showing the effect can also be obtained when training the innate immune system with a virus. (8)
2. All-cause mortality rates dropped 26-49% after introducing massive measles vaccination.(9)
3. COVID-19 case fatality rates among young children have been 1/1000 from those in adults, even in countries with no standard BCG vaccination. However, globally young children receive between 10 to 15 viral vaccines before the age of six.

Thus, with the here presented cases we support the AMS declaration that MMR vaccination, as a preventive measure, might reduce the severity of COVID-19, although we differ in our view on the mechanisms by which we hypothesize this happens. Though randomized, clinical and mechanistic trials shall be needed to unravel this topic, taking in consideration there are hardly any safety concerns, we maintain our positive attitude toward MMR vaccination during this pandemic.

Abbreviations

BCG: Bacillus Calmette-Guérin

COVID-19: Coronavirus disease-2019

MMR: mumps-measles-rubeola

NOD: Nucleotide-binding oligomerization domain-containing protein

RT-PCR: reverse transcription polymerase chain reaction

Th: T helper-cell

TLR: Toll-like receptor

TNF-α: Tumor necrosis factor alpha

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