

Incidence and Severity of COVID-19 with the use of the MMR Vaccine before or after the COVID-19 Vaccine

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ABSTRACT

Introduction: The MMR vaccine has been shown by several studies over the years to have a potent effect on heterologous immunity. The reduction in mortality and respiratory and gastrointestinal diseases in childhood has been consolidated with recent studies demonstrating a better evolution of COVID-19 with the use of this vaccine. Stimulation of innate immunity by the MMR vaccine can be very useful, both used alone or in association with other vaccines, especially those for COVID-19. **Objectives:** To evaluate the decrease in the incidence of infection or severity of COVID-19 with the use of the MMR vaccine before and after the use of specific vaccines against COVID-19. **Methods:** This extension analysis followed 120 volunteer healthcare professionals aged 18 to 60 who received the MMR vaccine before the specific COVID-19 vaccine and 73 volunteers who used the MMR vaccine after the COVID-19 vaccine. Visits to the Research Center were carried out at an average interval of 4 weeks for 12 weeks. The diagnosis of COVID-19 was performed using the RT-PCR technique for the SARS-CoV-2 virus. **Results:** The most used vaccine against COVID-19 was Coronavac in 59.1%. A total of 44 cases of COVID-19 were diagnosed (20% of the sample), the vast majority of which were mild cases (70.5%). There was no difference in the incidence and severity of COVID-19 in health professionals who used the MMR vaccine before or after the specific vaccine against the SARS-CoV-2 virus (Coronavirus or AstraZeneca). **Conclusion:** The incidence and severity of COVID-19 does not differ with the use of the MMR vaccine before or after the specific vaccine against COVID-19.

Keywords: COVID-19; Nasopharyngeal; qRT-PCR; Glycoprotein

INTRODUCTION

When the measles vaccine was introduced in various countries of the world (1970s-80s), large reductions in infant mortality of 40% or more were observed (1-6). The protective effect was much greater than expected given the reduction in measles mortality. These observations suggested that the measles vaccine could have beneficial protective effects against infections other than measles (7). This non-specific immune response produces a potent protective barrier that can prevent cell invasion by another virus (1,8,9). A vaccine with a live and attenuated microorganism can stimulate the innate immune response, whose repeated exposure to the antigen (training of the innate immune response) (10-13) prolongs the time of action of this immune response (memory of the innate immune response) and, consequently, protection for other infections (heterologous immunity) for a longer time (14-17). However, this stimulus will provide protection for a limited period of time. Therefore, memory induction of innate immunity, although useful, is only an emergency action to protect against infections. Even if this effect is for a limited period of time, it can greatly contribute to reducing the spread of infection in the early stages of a pandemic and/or reducing the severity of the disease, preventing hospitalizations and deaths (18-20).

We recently published a clinical trial with more than 400 health professionals evaluating the action of the MMR vaccine on the evolution

of COVID-19. The use of at least one dose of the MMR vaccine has shown a significant reduction in symptomatic COVID-19 by 42% and disease progression by 76% and 50% and 78% with two doses, respectively (21). This possible heterologous immunity of the MMR vaccine may be associated with the potent stimulation of innate immunity, leading to a decrease in the viral load by cellular immunity (2-6,18,22-25) and a possible action of humoral immunity by some similarities between the glycoproteins of the viruses of measles and rubella with SARS-CoV-2 (26,27) and the action of antibodies against mumps (28).

The aim of this study was to assess whether there is any difference in the incidence and evolution of COVID-19 with the use of the MMR vaccine before or after the specific vaccine against SARS-CoV-2, particularly Coronavac and AstraZeneca.

METHODOLOGY

Study Design and Participants

We recently published the effect of the MMR vaccine on the evolution of COVID-19 (MMRCoV Study) in 424 health professionals in the greater Florianópolis region (Santa Catarina – Brazil), evaluating heterologous immunity by stimulating innate memory immunity. During this 6-month analysis (through visit 7), starting the study in July 2020, we observed that the MMR vaccine reduced symptomatic

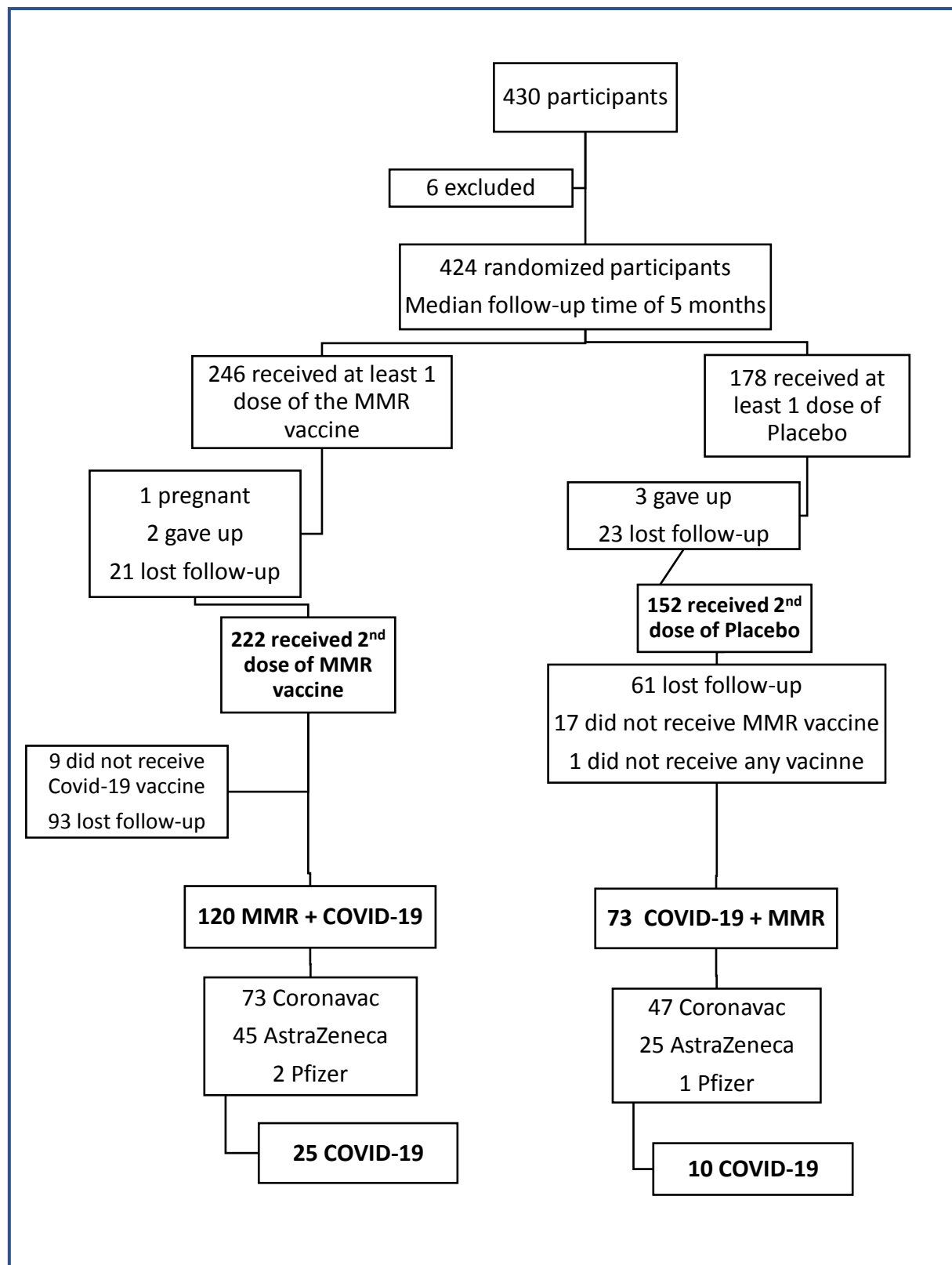
COVID-19 and prevented its progression. It was further demonstrated that the MMR vaccine was completely safe in this cohort of men and women aged 18 to 60 years (21).

In February 2021, specific vaccination against COVID-19 began in Brazil and health professionals were a priority group at the beginning of the vaccination campaign. Therefore, we did not have the opportunity to assess the long-term immune response, since most volunteers received Coronavac, Pfizer or AstraZeneca vaccines during this period. As described in the Protocol, with confirmation of the effectiveness of the MMR vaccine against COVID-19, it was offered to all study volunteers who received placebo. One question that we seek to answer with the second stage of this study is whether there is any difference in the evolution of COVID-19 with the use of the MMR vaccine before or after the specific vaccines against the disease. As soon as the health professionals received the COVID-19 vaccine, the blinding of the study was opened and we revealed to which group they were allocated. The cohort that received placebo at the beginning of the study was vaccinated with the MMR vaccine, respecting the 4-week interval between the COVID-19 and MMR vaccines and 8 weeks for the two doses of the MMR vaccine.

In this second phase of the study, we followed 220 volunteers, 129 from the initial MMR cohort and 91 from the initial Placebo cohort. Of the 129 volunteers in the initial MMR cohort, nine did not receive any

specific vaccine against COVID-19 and 93 were lost to follow-up, with 120 volunteers being evaluated for the effectiveness of the association of MMR and COVID-19 vaccines. Of the 91 volunteers in the initial Placebo cohort, one volunteer did not receive any vaccine (neither MMR nor COVID-19), 17 did not receive the MMR vaccine and 61 were lost to follow-up, with 73 volunteers being evaluated for the effectiveness of the combination of COVID-19 vaccines and MMR (Fig. 1).

Fig. 1: Study flowchart in Phase 1 and 2.



Procedures

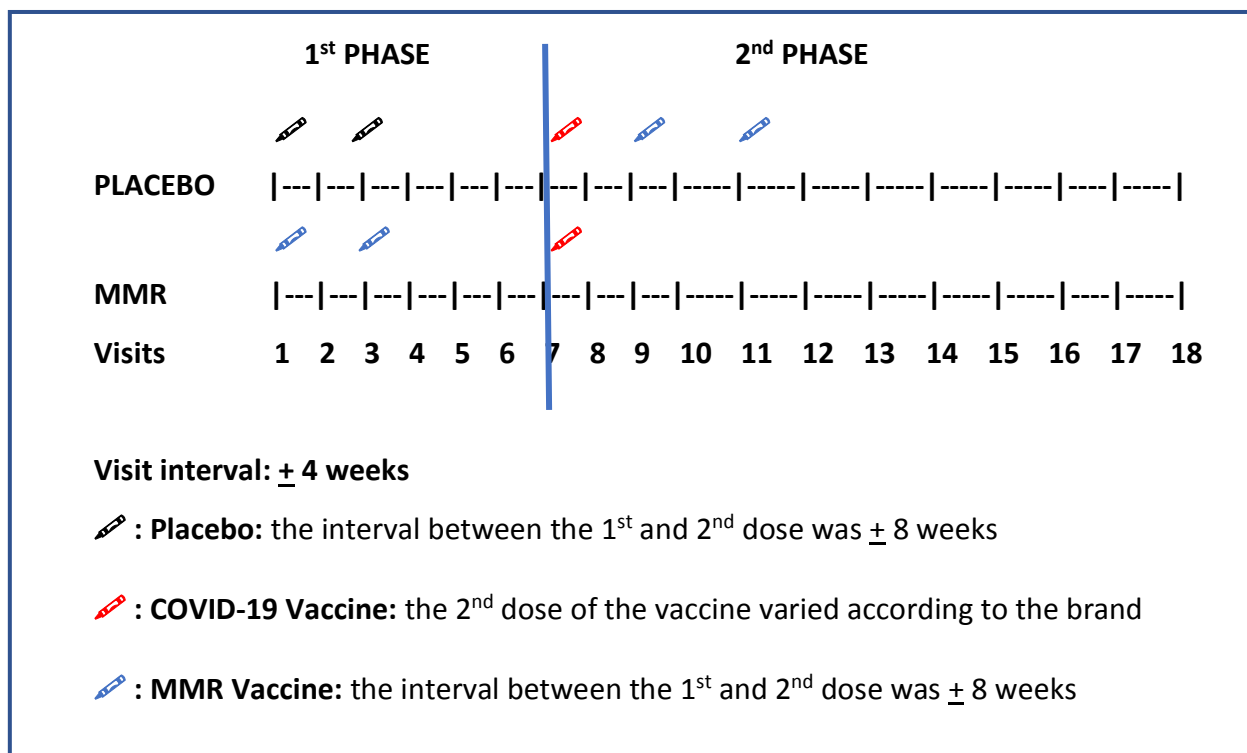
The second phase of the study involved monitoring 220 volunteers, especially those who used the MMR vaccine association (before or after) and specific vaccines against COVID-19. Thus, 193 volunteers (73 from the Placebo cohort and 120 from the MMR group) were followed for a period of 18 months (visit 17).

The volunteers visited the Research Center with an average interval of 4 weeks, where information was collected about their health, diagnosis of COVID-19, use of some medication and carried out the Rapid Test (IgG and IgM) for COVID-19 and collection oropharyngeal specimen for RT-PCR testing for SARS-CoV-2. The initial cohort that received placebo received two doses of the MMR vaccine, with an average interval of 8 weeks (Fig. 2).

A case, for the primary endpoint, was defined as a volunteer with a positive RT-PCR test for SARS-CoV-2, regardless of being symptomatic or not. To assess the severity of cases, we classified COVID-19 into 4 groups (29,30): 1) Asymptomatic: positive RT-PCR, absent symptoms; 2) Mild: positive RT-PCR, mild respiratory or clinical symptoms, with home follow-up; 3) Moderate: positive RT-PCR and respiratory or clinical symptoms that required non-symptomatic treatment such as anticoagulation, corticosteroid therapy and antibiotic therapy for pneumonia or hospitalization and 4) Severe: positive RT-PCR with

respiratory symptoms or other complications that required admission to the Unit intensive care or evolved to death.

Fig. 2: Procedures and visits in Phase 1 and 2 of the study.



Efficacy

The first outcome analyzed was the efficacy of the MMR + COVID-19 and COVID-19 + MMR vaccine combination in preventing RT-PCR-confirmed SARS-CoV-2 infection in participants with or without symptoms. The second outcome analyzed was the assessment of the severity of COVID-19 in these two cohorts.

Statistical analysis

The efficacy of the MMR vaccine combination before or after the specific COVID-19 vaccine in preventing COVID-19 and/or reducing severity was demonstrated by calculating VE as $(1-RR) * 100$, where the relative risk (RR) was defined as the proportion of individuals with COVID-19 in Cohort 1 (MMR vaccine + COVID-19 vaccine) to the rate of individuals with COVID-19 in Cohort 2 (COVID-19 vaccine + MMR vaccine).

Efficacy would be demonstrated if the lower limit of the 95% confidence interval (CI) of vaccine combination efficacy was greater than 0%. The primary outcome analyzed was the incidence of COVID-19 and the secondary outcome, the severity of the disease in both cohorts.

RESULTS

220 volunteers were followed, 129 from the initial MMR cohort and 91 from the Placebo cohort. Of the MMR cohort, 120 received a specific vaccine against COVID-19, while 9 volunteers did not want to receive the specific vaccine, having only the MMR at the beginning of the study.

In the Placebo cohort, 73 volunteers received the specific vaccine for COVID-19 and then the two doses of the MMR vaccine, respecting the interval between vaccines, according to the manufacturer. The interval

between MMR vaccine doses was + 8 weeks. 17 volunteers did not receive the MMR vaccine and one did not receive either the COVID-19 vaccine or the MMR vaccine.

In this follow-up period, from visit 8 to 18 (with interval of \pm 4 weeks), 951 clinical appointments were performed, 396 in the Placebo cohort and 555 in the MMR cohort.

The COVID-19 vaccine most used by healthcare professionals in the study was Coronavac (130 volunteers – 59.1%), followed by AstraZeneca with 77 volunteers (35%).

44 cases of COVID-19 were diagnosed (20% of the sample), with the vast majority of mild cases (70.5%). See Table 1.

Table 1: Evaluation of volunteers and number of clinical appointments in the phase 2 of the MMRCoV Study in healthcare professionals.

	FREQUENCY	
	n	%
VOLUNTEERS		
MMR Cohort	129	58.6
- MMR + COVID-19	120	93.0
- MMR	09	7.0
Placebo Cohort	91	41.4
- COVID-19 + MMR	73	80.4
- COVID-19	17	18.5
- Placebo	01	1.1
TOTAL	220	100
CLINICAL APPOINTMENTS		
Placebo Cohort	396	41.6
MMR Cohort	555	58.4
TOTAL	951	100
COVID-19 VACCINE		
Coronavac	130	59.1
AstraZeneca	77	35.0
Pfizer	03	1.4
None	10	4.5
COVID-19		
Yes	44	20.0
No	176	80.0
COVID-19 SEVERITY		
Asymptomatic	12	27.3
Mild	31	70.5
Moderate	01	2.2

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Regarding the number of cases of COVID-19 in the 951 clinical appointments, we observed that there was no difference in the incidence of the disease in the two cohorts (MMR + COVID-19 and COVID-19 + MMR) ($p=NS$). See Table 2. The same was observed when we evaluated the 220 study participants separately, with 21% in the

MMR + COVID-19 cohort and 16.4% in the COVID-19 + MMR cohort (p=NS). See Table 3.

Table 2: COVID-19 cases in the 951 clinical appointments of the phase 2 of the MMRCov study in healthcare professionals

VACCINE	COVID-19				TOTAL		p
	YES		NO		n	%	
	n	%	n	%			
MMR + COVID-19	27	5.1	504	94.9	531	55,8	NS
COVID-19 + MMR	10	4.7	202	95.3	212	22,3	
MMR	03	13.0	20	87.0	23	2.4	
COVID-19	04	2.5	158	97.5	162	17.0	
PLACEBO	00	0	23	100	23	2.5	
TOTAL	44	5.5	907	94.5	951	100	

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Table 3: COVID-19 cases in the 220 volunteers in the phase 2 of the MMRCov study in healthcare professionals

VACCINE	COVID-19				TOTAL		p
	YES		NO		n	%	
	n	%	n	%			
MMR + COVID-19	25	21.0	95	79.0	120	54.5	NS
COVID-19 + MMR	12	16.4	61	83.6	73	33.2	
MMR	03	33.3	06	66.7	09	4.1	
COVID-19	04	23.5	13	76.5	17	7.7	
PLACEBO	0	0	01	100	01	0.5	
TOTAL	44	20.0	176	80.0	220	100	

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When we evaluated the initial cohort that received the MMR vaccine and later the COVID-19 vaccine, we did not observe any statistical difference between the cases of COVID-19 and the type of vaccine used (Coronavirus 27.4% vs AstraZeneca 15.5%) (p =NS). The evaluation

of the use of the Pfizer vaccine was not carried out by the very small number of users (two). The same occurred with the initially Placebo cohort that received the COVID-19 vaccine and then the MMR vaccine (Coronavirus 17.1% vs AstraZeneca 8%) (p=NS). See Table 4.

Table 4: COVID-19 cases according to the type of COVID-19 vaccine and the time when the MMR vaccine was administered in the phase 2 of the MMRCov study in healthcare professionals

VACCINE	COVID-19				TOTAL		p
	YES		NO		n	%	
	n	%	n	%			
MMR + CORONAVAC	20	27.4	53	72.6	73	33.2	NS
MMR + ASTRAZENECA	07	15.5	38	84.5	45	20.5	
MMR + PFIZER	0	0	02	100	02	0.9	
CORONAVAC + MMR	08	17.1	39	82.9	47	21.4	NS
ASTRAZENECA + MMR	02	8.0	23	92.0	25	11.4	
PFIZER + MMR	0	0	01	100	01	0.4	
CORONAVAC	02	20.0	08	80.0	10	4.5	NS
ASTRAZENECA	02	28.6	05	71.4	07	3.2	
MMR	03	33.3	06	66.7	09	4.1	
PLACEBO	0	0	01	100	01	0.4	NS
TOTAL	44	20.0	176	80.0	220	100	

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We had no cases of severe COVID-19 and only one case of moderate in the MMR + COVID-19 cohort. The vast majority of volunteers had mild cases (65.4%). Asymptomatic cases accounted for 32.7%. There was no statistically significant difference regarding the severity of COVID-19 and the use of the MMR vaccine before or after the specific COVID-19 vaccine (p=NS). See Table 5. When we evaluated the type of COVID-19 vaccine (Coronavac or AstraZeneca), we observed that there was no difference in the severity of COVID-19 between them and

between the MMR + COVID-19 and COVID-19 + MMR cohorts (p= NS). See Table 6.

Table 5: Severity of COVID-19 according to the cohort that used the MMR Vaccine before and after the COVID-19 vaccine in the phase 2 of the MMRCov study in healthcare professionals

VACCINE	COVID-19						TOTAL		p
	ASYMPTOMATIC		MILD		MODERATE		n	%	
	n	%	n	%	n	%			
MMR + COVID-19	06	24.0	18	72.0	01	4.0	25	56.8	NS
COVID-19 + MMR	05	41.7	07	58.3	00	0	12	27.3	
MMR	01	66.7	02	33.3	00	0	03	6.8	
COVID-19	00	44.4	04	55.6	00	0	04	9.1	
TOTAL	12	32.7	31	65.4	01	1.9	44	100	

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Table 6: Severity of COVID-19 according to the COVID-19 vaccine and timing of the MMR vaccine in the phase 2 of the MMRCov study in healthcare professionals

VACINNE	COVID-19						TOTAL		p
	ASYMPTOMATIC		MILD		MODERATE		n	%	
	n	%	n	%	n	%			
MMR + CORONAVAC	03	15.0	16	80.0	01	5,0	20	41,0	NS
MMR + ASTRAZENECA	03	42.9	04	57.1	00	0	07	15,9	
MMR + PFIZER	00	0	00	0	00	0	00	0	
CORONAVAC + MMR	04	50.0	04	50.0	00	0	08	20,5	
ASTRAZENECA + MMR	01	50.0	01	50.0	00	0	02	6,8	
PFIZER + MMR	00	0	00	0	00	0	00	0	NS
CORONAVAC	00	0	02	100	00	0	02	4,5	
ASTRAZENECA	00	0	02	100	00	0	02	4,5	
MMR	01	33.3	02	66,7	00	0	03	6,8	
TOTAL	12	32.7	31	65,4	01	1,9	44	100	

MMRCov Study – HU/UFSC 220-2023.

DISCUSSION

In a previous double-blind, randomized, placebo-controlled study (RCT), we demonstrated that the use of at least one dose of the MMR vaccine demonstrated a significant reduction of symptomatic COVID-19 by 42% and disease progression by 76%, confirming several previous studies that observed a reduction in infant mortality, respiratory and gastrointestinal infections, through heterologous immunity triggered by the stimulation of innate immunity by attenuated vaccines (1,7,12,14,17,18,31-41) and specifically with the MMR vaccine (2-6,18,22-25,30). Unfortunately, the duration of protection from heterologous immunity is still not well defined. In this study, the median follow-up was 5 months and it was not possible to assess the long-term effectiveness because the health professionals who volunteered for the study were immediately vaccinated with the specific vaccines against COVID-19. In this second phase of the study, we followed the volunteers for more 12 months, now evaluating whether the order of use of the MMR vaccine (before or after the COVID-19 vaccine) showed any difference in the incidence and evolution of the disease. This is the first clinical study to assess whether the order of use of the MMR vaccine (before or after the COVID-19 vaccine) makes any difference in disease progression.

Even after using specific vaccines against COVID-19, the percentage of positive cases was high, at 20%. This high percentage is probably

justified because the participants are all from the health area and many work on the front lines. In a systematic review and meta-analysis of the prevalence of COVID-19 in health professionals diagnosed through RT-PCR, Gómez-Ochoa observed a high prevalence of infected people in the health area, of 11% (42).

Although the percentage of COVID-19 was lower (16%) in the cohort that received the MMR vaccine after the COVID-19 vaccine (compared to the 21% that received it before), this difference was not significant ($p=NS$). However, it is possible to infer that the heterologous immunity response is more robust in the cohort that received the MMR vaccine before the COVID-19 vaccine due to the greater interval between the two and there was no difference in the efficacy. Several studies have shown, however, that possibly the memory of innate immunity (stimulated by innate immunity training) can last for a year or more (17,20,43).

Most cases of COVID-19 have been mild or asymptomatic. Although asymptomatic COVID-19 was more frequent in the cohort that used the MMR vaccine after the COVID-19 vaccine (41.7% vs 24%), this difference was not statistically significant ($p=NS$). The same reasoning that we used in relation to the incidence of COVID-19 applies here. It can be postulated that when someone has a potent immune response and encounters the SARS-CoV-2 virus, a strong activation of local innate and adaptive immune responses keeps viremia in check, leading

to low inflammation and systemic recovery. In contrast, in individuals with a defective immune response, due to old age or comorbidities, unrestricted viral replication leads to high concentrations of the virus, which in turn trigger hyperinflammation and serious complications such as severe acute respiratory syndrome and death (34,44). In an observational clinical study with 255 volunteers vaccinated with MMR vaccine, the authors observed that all 36 cases of COVID-19 in this group had only mild symptoms (20). Some justifications that demonstrate that the MMR vaccine could have some action against COVID-19 are: 1) potent stimulation of the innate immune response and its memory (10-13). Recent reports indicate that COVID-19 can suppress the innate immune response (45); 2) the MMR vaccine viruses and the coronavirus are RNA viruses and, perhaps, this could further benefit the stimulation of the innate immune response using this vaccine (14); 3) 30 amino acid sequence homology between the SARS-CoV-2 Spike glycoprotein (PDB:6VSB) and measles virus fusion glycoproteins (PDB:5YW_B) and rubella virus envelope glycoproteins (PDB:4ADG_A). These regions could be antigenic epitopes to stimulate humoral immunity, whose antibodies could protect against COVID-19. This could be one of the explanations for the lower involvement of children with COVID-19 (26,27); 4) the macrodomains of the SARS-CoV-2 virus and the rubella virus have an identical amino acid sequence in 29%. Hypothetically, these SARS-CoV-2 macrodomains could be recognized by rubella antibodies and provide a certain degree

of protection. One study demonstrated that rubella antibody (IgG) levels increased in patients with COVID-19, similar to cases of a second rubella infection (27); 5) significant evidence of an inverse correlation between mumps antibody levels and COVID-19 severity, i.e., the higher the mumps IgG antibody concentration, the lower the COVID-19 severity (28).

The incidence of COVID-19 was lower in health professionals who used the AstraZeneca COVID-19 vaccine, both after the MMR vaccine (15.5%) and before (8%), when compared to the Coronavac vaccine (27.4% and 17.1%, respectively). The same was observed in relation to the severity of the disease, both for asymptomatic cases and for mild cases. However, these differences were not statistically significant ($p=NS$). Efficacy studies of vaccines against COVID-19 show very similar results, although prevention of symptomatic and severe disease has been shown to be greater for AstraZeneca (46).

This study had many limitations. The number of participants was small, with many losses to follow-up of the original study. The median follow-up was 12 months and this prevented us from having a more adequate assessment of the duration of action of the heterologous immunity. It was not possible to assess the cellular immune response and viral load of participants who had COVID-19. Certainly, if we had a control cohort of health professionals without the use of any vaccine, it would be possible to better assess long-term immunity. The specific

vaccines used by the study participants were, in almost all cases, Coronavac and AstraZeneca and these results are not necessarily the same for other vaccines. The age range evaluated was 18-60 years and we cannot guarantee that the observed results may be the same in people above and below this age.

The results of this study demonstrated that the MMR vaccine before or after the COVID-19 vaccine had virtually the same results regarding the incidence and severity of COVID-19. As in the previous study it was proved that the MMR vaccine reduces the incidence of symptomatic COVID-19 and its evolution (21), it is quite possible that this action has been maintained throughout this study period and to say that the action of the heterologous immunity of the MMR vaccine is of at least 18 months. As this result is related to the stimulation of heterologous immunity, we can dazzle that the MMR vaccine could be useful in cases of new epidemics/pandemics as an emergency measure, until specific treatments or vaccines for each case are made available to the general population. Faced with the world scenario we are observing, especially with the new variants, it is very likely that the MMR vaccine, due to its mechanism of action, will continue to protect against new and future mutations of SARS-CoV-2. However, it is important to note that the MMR vaccine does not replace specific vaccines against COVID-19.

CONCLUSION

There was no difference in the incidence and severity of COVID-19 in healthcare workers who used the MMR vaccine before or after the specific vaccine against the SARS-CoV-2 virus (Coronavirus or AstraZeneca) and possibly the heterologous immunity from the MMR vaccine lasted at least these 18 months of follow-up, being 6 months in the original study and 12 months in this extension study.

Declaration of competing interests: All authors declare no competing interests.

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Author contributions

Edison Natal Fedrizzi: Conceptualization, Methodology, Writing original draft preparation, Project administration; Juliana Balbinot Reis Girondi:

Supervision, Investigation; Aldanéa Norma de Souza Silvestrin: Supervision, Investigation; Alberto Trapani Junior: Investigation; Maria Veronica Nunes: Investigation, Funding acquisition;

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References

1. Higgins JP, Soares-Weiser K, Lopez-Lopez JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ*. 2016;355:i5170.
2. Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. *Lancet* 1981;1:764-7.
3. Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, Helm-Petersen NC, et al. Child mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200.
4. Holt EA, Boulos R, Halsey NA, Boulos IM, Boulos C. Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics* 1990;85:188-94.

5. Clemens JD, Stanton BF, Chakraborty J, Chowdhury S, Rao M, Ali M. Measles vaccination and childhood mortality in rural Bangladesh. *Am J Epidemiol* 1988;128;1330-9.
6. Koenig MA, Khan MA, Wojtyniak B, Clemens JD, Chakraborty J, Fauveau V, et al. The impact of measles vaccination upon childhood mortality in Matlab, Bangladesh. *Bull World Health Organ* 1990;68:441-7.
7. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol* 2013;34:431-9.
8. Biswas J. Can Oral polio vaccine offer protection against the Coronavirus? Eminent virologist believes it can. *Science* April 28, 2020. Available in https://www.ibtimes.sg/can-oral-polio-vaccine-offer-protection-against-coronavirus-eminent-virologist-believes-it-can-43931?fbclid=IwAR06zr3ZnNsZyuGEr2CturIQNc3OsBdAcjyr_cdweGB22A1FoTbGzGeFOVs [accessed May 15, 2023].
9. BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE). Available in <https://clinicaltrials.gov/ct2/show/NCT04327206>. [accessed May 15, 2021].
10. Mulder WJM, Ochando J, Joosten LAB, Fayad ZA, Netea MG. Therapeutic targeting of trained immunity. *Nature Review Drug Discovery*. Available in <https://doi.org/10.1038/s41573-019-0025-4>. [accessed June 18, 2022].
11. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol* 2020;20(6):375-88. <https://doi.org/10.1038/s41577-020-0285-6>.
12. Shann F. The heterologous (non-specific) effects of vaccines: implications for policy in high-mortality countries. *Trans R Soc Trop Med Hyg* 2015; 109: 5-8. <https://doi.org/10.1093/trstmh/tru161>.

13. Benn CS, Fisker AB, Whittle HC. Aaby P. Revaccination with live attenuated vaccines confer additional beneficial nonspecific effects on overall survival: a review. *E Bio Medicine* 2016;10:312–7.
14. Chumakov K, Benn CS, Aaby P, Kotttilil S, Gallo R. Can existing live vaccines prevent COVID-19? Live vaccines can prevent unrelated infections and may temporarily protect against COVID-19. *Science* 2020;368(6496):1187-8.
15. Voroshilova MK. Potencial use of nonpathogenic enteroviruses for control of human diseases. *Progr Med Virol* 1989;36:191-202.
16. Higgins JPT, Weiser KS, López-López JA, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;355:i5170. <https://doi.org/10.1136/bmj.i5170>.
17. Rieckmann A, Villumsen M, Sorup S, Haugaard LK, Ravn H, Roth A, et al. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971–2010. *Int J Epidemiol* 2017;46(2):695–705. <https://doi.org/10.1093/ije/dyw120>.
18. Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, Curtis N, van Crevel R, van de Veerdonk FL, Bonten M. Trained immunity: a tool for reducing susceptibility and severity of SARS-CoV-2 infection. *Cell* 2020;181(5):969-77.
19. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Oosting M, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell Host & Microbe* 2018;3:89–100.
20. Larenas-Linnemann DE & Rodriguez-Monroy F. Thirty-six COVID-19 cases preventively vaccinated with mumps-measles-rubella vaccine: All mild course. *Allergy* 2020;00:1-5. <https://dx.doi.org/10.1111/all.14584>.
21. Fedrizzi EN, Reis Girondi JB, Sakae TM, Steffens SM, de Souza Silvestrin AN, Claro GS, et al. 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. J Clin Trials 2022; S15:004.

22. Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and child mortality. Lancet 1981;ii:93.

23. Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child mortality: a community study from Guinea-Bissau. J Infect 1984;8:13-21.

24. Aaby P, Samb B, Simondon F, Knudsen K, Coll Seck AM, Bennett J, et al. Divergent mortality for male and female recipients of low-titre and high-titre measles vaccines in rural Senegal. Am J Epidemiol 1993;138:746-55.

25. 36. Aaby P, Martins CL, Garly ML, Bale C, clinician, Andersen A, Aaby AR et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. BMJ 2010;341:c6495. <https://doi.org/10.1136/bmj.c6495>.

26. Sidiq KR, Sabir DK, Ali SM, Kodzius R. Does early childhood vaccination protect against COVID-19. Front Mol Biosci 2020;7:120. <https://dx.doi.org/10.3389/fmolb.2020.00120>.

27. Young A, Neumann B, Menezes RF, Reyahi A, Joannides A, Modis Y, Franklin RJM. Homologous protein domains in SARS-CoV-2 and measles, mumps and rubella viruses: preliminary evidence that MMR vaccine might provide protection against COVID-19. medRxiv 2020 preprint [https:// dx.doi.org/10.1101/2020.04.10.20053207](https://dx.doi.org/10.1101/2020.04.10.20053207).

28. Gold JE, Baumgartl WH, Okyay RA, Licht WE, Fidel PL, Jr et al. 2020. Analysis of measles-mumps-rubella (MMR) titers of recovered COVID-19 patients. mBio 11:e02628-20. <https:// dx.doi.org/10.1128/mBio.02628-20>.

29. Capaccione KM, Yang H, West E, et al. Pathophysiology and imaging findings of COVID-19 infection. An organ system based review. Acad Radiol 2021;28(5):595-607.

30. Hartfield, J, Morley, D. Efficacy of Measles Vaccine. J. Hyg. (Lond.) 1963;61:143–7.
31. Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, Pollard AJ et al. Harnessing the beneficial heterologous effects of vaccination. Nat Rev Immunol 2016;16:392–400.
32. Aaby P, Benn CS. Developing the concept of beneficial non-specific effect of live vaccines with epidemiological studies. Clin Microbiol and Infection 2019;25(12):1459-67.
33. Cauchi S, Locht C. Non-specific Effects of Live Attenuated Pertussis Vaccine Against Heterologous Infectious and Inflammatory Diseases. Front Immunol 2018;9:2872. <https://doi.org/10.3389/fimmu.2018.02872>.
34. WHO. Nonspecific effects of vaccines on childhood mortality. Wkly Epidemiol Rec 2014;89:233–5.
35. Wardhana O, Datau EA, Sultana A, Mandang V V, Jim E. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. Acta Med Indones 2011;43:185–190.
36. Ohnishi T, Nakayama K, Fukushima T, Chiba H, Sasaki H. Prevention of elderly pneumonia by pneumococcal, influenza and BCG vaccinations. Japanese J Geriatr 2005;42:34–6.
37. Brook B, Harbeson DJ, Shannon CP, Cai B, He D, Ben-Othman R, Francis F et al. BCG vaccination–induced emergency granulopoiesis provides rapid protection from neonatal sepsis. Science Translational Medicine 2020;12(542):eaax4517. <https://doi.org/10.1126/scitranslmed.aax4517>.
38. Andersen A, Fisker AB, Rodrigues A, Martins C, Ravn H, Lund N, et al. National Immunization Campaigns with Oral Polio Vaccine Reduce All-Cause Mortality: A Natural Experiment within Seven Randomized Trials. Front. Public Health 2018;6(13). <https://doi.org/10.3389/fpubh.2018.00013>.

39. Upfill-Brown A, Taniuchi M, Platts-Mills JA, Kirkpatrick B, Burgess L S, Oberste MS, et al. Nonspecific Effects of Oral Polio Vaccine on Diarrheal Burden and Etiology Among Bangladeshi Infants. Clin Infect Dis 2017;65:414-9.
40. Seppala E, Viskari H, Hoppu S, Honkanen H, Huhtala H, et al. Viral interference induced by live attenuated virus vaccine (OPV) can prevent otitis media. Vaccine 2011;29(47):8615-8.
41. Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. Am J Epidemiol 1995;142:643-52.
42. Gómez-Ochoa SA, Franco OH, Rojas LZ, Raguindin PF, Roa-Díaz ZM, Wyssmann BM. COVID-19 in Healthcare Workers: A Living Systematic Review and Meta-analysis of Prevalence, Risk Factors, Clinical Characteristics, and Outcomes. Am J Epidemiol 2021;190(1):161-75. <https://dx.doi.org/10.1093/aje/kwaa191>.
43. Kleinnijenhuis J, Quintin J, Preijers F, Ben CS, Joosten LAB, Jacobs C, et al. Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. J Innate Immun 2014;6(2):152-8.
44. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
45. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cel & Molecular Immunol 2020;17:533-5.
46. Fedrizzi EN. Vacina contra a COVID-19. In Schlemper Jr BR. COVID-19 – A Guerra da desinformação. O desafio da ciência, bioética e socialização do saber. Ed Appris, 2022. 1.ed., Curitiba. Pg 427-447.