Vaccine: X 10 (2022) 100147

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

COVID-19 susceptibility and vaccination coverage for measles, rubella and mumps in students and healthcare workers in Trieste hospitals (NE Italy)

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ARTICLE INFO

Article history:
Received 29 July 2021
Received in revised form 4 February 2022
Accepted 16 February 2022
Available online 25 February 2022

ABSTRACT

Background: Measles, mumps, and rubella (MMR) vaccines have been suggested as preventive measures to protect subjects from the worst sequelae of COVID-19 infection because neutralizing antibodies can cross-react with other viruses.
Aim: To verify COVID-19 infection in MMR vaccinated and non-vaccinated healthcare workers and medical students in Trieste Hospitals.
Results: Nurse aids resulted in significantly more infections than structured physicians (OR 1.80; 95% CI 1.14–2.80) while students resulted in less infections (OR, 0.66; 95% CI 0.43–1.01). The presence of an MMR vaccination was inversely associated with COVID-19 (OR, 0.77; 95% CI 0.61–0.96) but only in univariate analysis. In the multivariable logistic regression analysis, MMR vaccination lost statistical significance (OR, 0.86; 95%CI 0.62–1.20).
On 13 HCWs hospitalized for COVID-19, 11 resulted not vaccinated for MMR.
Discussion: Our study found a mild, non-significant reduction in SARS-CoV-2 infections in workers vaccinated with MMR.

Introduction

In June 2020, the American Society for Microbiology (ASM) hypothesized that the measles, mumps, and rubella (MMR) vaccine could serve as a preventive measure to protect subjects from the worst sequelae of COVID-19 infection [1]. In the literature, there is evidence that unrelated live attenuated vaccine by the stimulation of "trained" nonspecific innate immune cells improves host responses against subsequent infections and thus could produce nonspecific protection against infections unrelated to the target pathogen [2,3]. Although there are still conflicting opinions on this matter, much evidence supports this concept. For example, it has been reported in the sailors on the U.S.S. Roosvelt that all vaccinated with MMR vaccine, those positive for Sars-CoV-2 have developed all mild symptoms, and only one of them needed hospitalization [1]. Moreover, each vaccine induces a variety of antibodies directed against the virus. MMR vaccines could induce the formation of neutralizing antibodies that cross-react with other viruses, known as the overlapping of vaccine epitopes and amino acid residues between Sars-Cov-2, measles, and rubella glycoproteins [4]. There have been reports of patients infected with Sars-Cov-2 who developed neutralizing antibodies against measles [5]. In addition, a significant inverse correlation has been reported between mumps IgG titers due to MMR vaccine and COVID-19 severity, not age-related [6], and between COVID-19 severity and MMR vaccination status (p = 0.013) [7].

MMR vaccines may protect against COVID-19 diseases [8–12] or may reduce the severity of novel coronavirus diseases, observing that COVID-19 infection and deaths were lower in countries with recent and large-scale MMR vaccination campaigns. Moreover, a recent study suggested that population-level associations may be further confounded by differences in structural health systems and policies [13]. The molecular theory is based on the overlapping of vaccine epitopes and amino acid residues between the spike glycoprotein of SARS-CoV-2 virus and the fusion glycoprotein of measles virus and the envelope glycoprotein of the rubella virus, which possibly results in children presenting with a milder version of COVIS-19 disease in contrast to adults [14]. In general, previous studies reported data on small numbers of subjects and found a

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https://doi.org/10.1016/j.jvacx.2022.100147
2590-1362/

significant inverse correlation between mumps titers related to the MMR vaccine and COVID-19 disease [6].

In Italy, MMR vaccination has been recommended for all children. The 2017–2019 National Vaccine Prevention Plan suggests the administration of two doses of MMR at 13–15 months and six years, respectively. In our hospital, to reduce the diffusion of vaccine-preventable diseases and promote vaccination [8–9], we evaluated serum antibodies for MMR and vaccination status in healthcare workers and students working or training in our hospital.

Purpose

This study investigated the association between COVID-19, vaccination rates, and antibody titers for measles, rubella, and mumps in students and health care workers in Trieste hospitals, which were routinely (at least monthly) screened for SARS-CoV-2 RNA detection in nasopharyngeal swabs using real-time polymerase chain reaction (RT-PCR).

Material and methods

Between March 2020 and February 2021, the Unit of Occupational Medicine at the University of Trieste was involved in contact tracing and active surveillance of SARS-CoV-2 among hospital employees and medical students [15]. Since March 1, 2020, workers in contact with COVID-19 patients or with respiratory symptoms have been tested for Sars-Cov-2 in nasopharyngeal and oropharyngeal swabs every 3 days since contact time. Since April 15, HCWs have been routinely tested (weekly or monthly, according to hazard classification) for Sars-Cov-2 in nasopharyngeal swabs, independent of contacts or symptoms. Symptoms were recorded on the day of swab positivity and every 3 days since the swab was negative through a phone interview considering fever >37.5 °C (yes/no), upper respiratory symptoms (yes/no), lower respiratory symptoms (yes/no), cough (yes/no), loss of taste and smell (yes/no), and gastrointestinal symptoms (yes/no).

The population studied consisted of 2829 health care workers and medical students for whom MMR vaccination status (obtained through digital records) and antibodies against rubella, measles, and mumps were collected in 2019 during periodical medical surveillance at the Clinical Unit of Occupational Medicine. Data on SARS-Cov-2 detection in nasopharyngeal swabs from March 2020 to February 2021 were available. Workers who were vaccinated against SARS-CoV-2 were excluded from the analysis.

Nasopharyngeal and oropharyngeal specimens were collected using the swab technique, and RNA was extracted and determined by rRT-PCR targeting the E, N, and RdRp genes of SARS-CoV-2, according to the CDC and Charité laboratory protocols [16]. The cycle threshold values of RT-PCR were used as qualitative indicators of the viral load of SARS-CoV-2 RNA in specimens, with lower cycle threshold values corresponding to higher viral copy numbers. A cycle threshold value of <30 was interpreted as positive for SARS-CoV-2 RNA.

Measles-specific IgG antibodies in the serum were detected using the chemiluminescent (CLIA) LIASON Measles IgG test (sensitivity, 94.7%; specificity, 97.4%). Subjects showing a measles-specific IgG level higher than 16.5 UA/mL were considered serologically immune, those with a level between 13.5 and 16.5 UA/mL were considered borderline and those with a level below 13.5 UA/mL were considered negative. Mumps-specific IgG was detected using chemiluminescence technology (CLIA) with the LIAISON Mumps IgG test (sensitivity, 98.5%; specificity, 98.2%). Subjects showing mumps-specific IgG antibody titers above 11 UA/mL were considered serologically immune; titers were borderline between 9 and 11 UA/mL and negative if they were lower than 9 UA/mL. Rubella-specific IgG was detected using chemiluminescent (CLIA) LIAISON Rubella IgG II test (sensitivity, 99.5%; specificity, 99.6%). Subjects with rubella-specific IgG levels > 10 UI/mL were considered positive, those with a level between 7 and 10 UI/mL were considered borderline, and those with a level < 7 UI/mL were considered negative.

Data analysis was performed using the STATA™ software (version 14.0; Stata Corp., LP, College Station, TX, USA).

Categorical data were cross-tabulated into k × k contingency tables and were statistically tested using the χ^2 test. Continuous data are reported as mean and standard deviation and were statistically tested using Student's *t-test*. COVID-19 as an outcome was analyzed by univariate logistic regression analysis, with sex, age (as a continuous variable), occupation (residence, nurse, nurse aid, others, and physician as reference), MMR vaccination (yes/no), IgG positive titers against rubella (yes/no), measles (yes/no), and mumps (yes/no) as independent variables. Factors associated with COVID-19 were investigated using multivariable regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from the coefficients and standard errors of logistic regression. Workers with missing data for relevant variables were excluded from the analysis (n = 245, 8.7%). A p-value of <0.05 was established as the limit of statistical significance.

The local Ethical committee approved the study (CEUR- 2020-Os-072) on 16.04.2020.

Results

A total of nine subjects, with a mean age of 38 ± 13.5 years, were studied. Of them, 922 (32.6%) were students. Their characteristics are reported in Table 1, considering COVID-19 infected and non-infected. The prevalence of infection was lower in administrative staff (5.1%) and laboratories (6.8%) and higher in medical departments (21.3%, p < 0.001). Nurses and nurse aids presented a higher prevalence of COVID-19 infection than other work tasks (16.1% and 20%, respectively). The medical students had a lower prevalence of COVID-19 (8.5%).

The prevalence of COVID-19 was lower in subjects who received at least two doses of MMR vaccination (9.4%) than in those who did not receive the vaccination (13.9%, p < 0.009).

Antibodies against measles, rubella, and mumps were present in 87.1%, 90.4%, and 88.1% of subjects, respectively, without differences between COVID-19 positive and negative subjects (Fig. 1). Analyzing HCWs and students for COVID-19 infection and MMR vaccination, we did not find a significantly lower prevalence of infection in vaccinated individuals, while we confirmed a lower prevalence of COVID-19 infection in students vaccinated (8.4%) or non-vaccinated (9.1%) compared to workers (14.3% and 14.1% in vaccinated or non-vaccinated, respectively).

COVID-19 symptoms were mild in workers and students, with lower respiratory symptoms in 10% of workers who required hospitalization in 13 subjects. Eleven (85%) were not vaccinated with MMR and ten were naturally immunized against measles. One patient received only one MPR dose and the other received two doses. The students reported only mild symptoms (upper respiratory symptoms, loss of smell, and taste).

Factors associated with COVID-19 positivity were analyzed using univariate logistic regression analysis (Table 2). Nurse aids resulted in significantly more infections than structured physicians (OR 1.80; 95% CI 1.14–2.80) while students resulted in less infections (OR, 0.66; 95% CI 0.43–1.01). All HCWs had a higher risk of being COVID-19 positive compared to students (OR 1.78; 95% CI 1.36–2.32). The presence of an MMR vaccination resulted in protection against COVID-19 (OR, 0.77; 95% CI 0.61–0.96) in the uni-

Table 1
Characteristics of the population studied.

	COVID-19 +	COVID-19 -	TOTAL	p
N	348 (12.3)	2461 (87.7)	2829 (100)	
WOMEN	228 (65.5)	1662 (67.5)	1890 (66.8)	ns
MEN	120 (34.5)	819 (32.5)	939 (33.2)	
MEAN AGE ± SD	39.4 ± 4	37.8 ± 13.5	38.0 ± 13.5	ns
Workplaces				
– Administration	2 (0.6)	37 (1,5)	39 (1.4)	0.001
– Surgical wards	51 (16.4)	418 (17.0)	469 (16.6)	
– Medical wards	145 (41.7)	537 (21.8)	682 (24.0)	
– Training in various wards	96 (27.6)	995 (40.4)	1091 (38.6)	
– Services	39 (11.2)	302 (12.3)	341 (12.0)	
– Laboratories	11 (3.2)	150 (6.1)	161 (5.7)	
– Logistic	4 (1.1)	42 (1.7)	46 (1.6)	
Work tasks				
– Physicians	35 (10.1)	252 (10.2)	287 (10.1)	0.01
– Residents	26 (7.5)	186 (7.6)	212 (7.5)	
– Nurses	101 (29.0)	528 (21.4)	629 (22.2)	
– Nurse aids	57 (16.4)	228 (9.3)	285 (10.1)	
– Students	78 (22.4)	844 (34.3)	922 (32.6)	
– Others	51 (14.6)	443 (18.0)	497 (17.6)	
MMR: doses				
0	176 (50.6)	1094 (44.4)	1270 (44.9)	0.05
1	37 (10.6)	259 (10.5)	296 (10.4)	
2	90 (25.9)	869 (35.3)	959 (33.9)	
3	3 (0.9)	11 (0.4)	14 (0.5)	

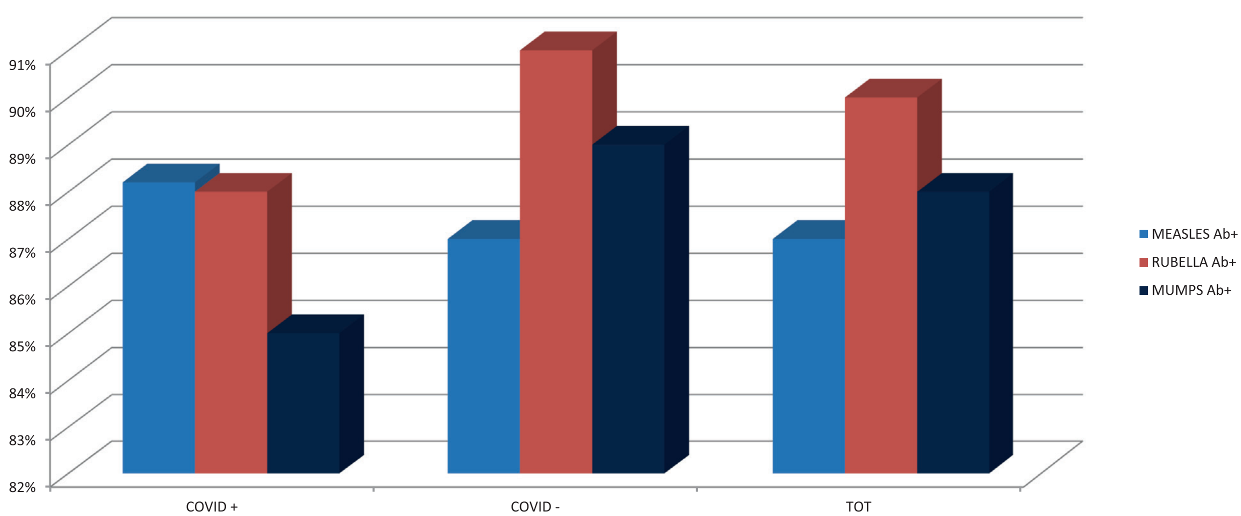

Fig. 1. MMR doses in our population and COVID-19 infection.

Table 2
Factors related to SARS-CoV-2 positivity evaluated with univariate and multivariable logistic regression. Association are reported as Odds Radio (OR) and 95% Confidence Intervals (CI). In bold are reported significant associations.

	UNIVARIATE	MULTIVARIABLE
Factors	OR (IC 95%)	OR (IC 95%)
Age	1.00 (1.00–1.01)	0.98 (0.97–1.00)
Male Sex	1.10 (0.84–1.35)	1.1 (0.86–1.40)
Work tasks		
Physician	1	
Resident	1.0 (0.58–1.72)	
Nurse	1.37 (0.91–2.10)	
Nurse aids	**1.80 (1.14–2.80)**	
Student	0.66 (0.43–1.01)	
Others	0.82 (0.52–1.30)	
MMR vaccination+	**0.77 (0.61–0.96)**	0.86 (0.62–1.20)
HCWs *vs* students	**1.78 (1.36–2.32)**	**2.01 (1.46–2.94)**
Measles Ab+	1.12 (0.78–1.61)	
Rubella Ab+	0.77 (0.53–1.11)	
Mumps Ab+	0.76 (0.53–1.10)	

variate analysis. No association was found between antibody titers for measles, rubella, mumps, and SARS-CoV-2. In the multivariable logistic regression analysis, HCWs were confirmed to be at a higher risk of being COVID-19 positive compared to students (OR 2.01, 95% CI 1.46–2.94), while the MMR vaccination protective effect was not statistically significant (Fig. 2).

Discussion

Our study investigated COVID-19, MMR vaccination, and IgG antibodies in serum for measles, rubella, and mumps in health care workers and students at the University Hospital of Trieste. Involved subjects underwent routinely the detection of SARS-Cov-2 in nasopharyngeal swabs, independently of symptoms or contact with COVID-19 patients, thou the screening performed permitted to have precise information on COVID-19 infection in our population.

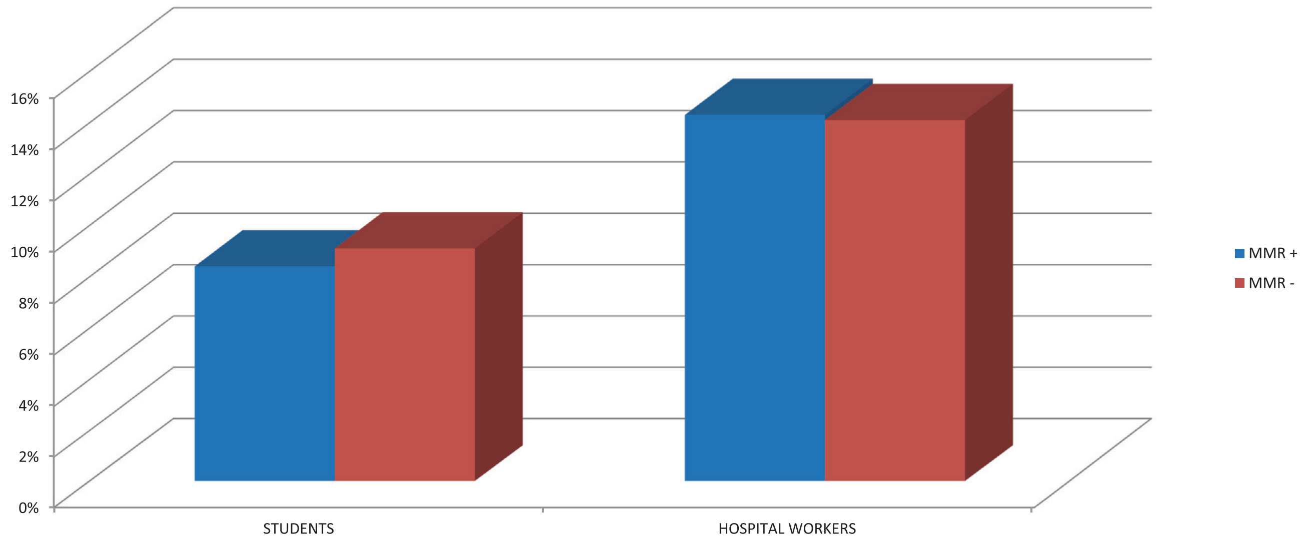

Fig. 2. MMR vaccination rates in students and in hospital workers.

We found a lower prevalence of COVID-19 in medical students compared to hospital workers, as younger subjects have a lower prevalence of COVID-19, according to other studies [9–12,17]. In the univariate logistic regression, COVID-19 infection was significantly lower in subjects vaccinated for MMR (OR = 0.77; CI95% 0.61–0.96), and HCWs presented an increased risk of SARS-CoV-2 infection compared to students (OR = 1.78; 95%CI 1.36–2.32), whereas no association was found with antibody titers for measles, rubella, and mumps. However, in the multivariable logistic regression, alysisthe MMR vaccination lost statistical significance, meaning that the risk of developing COVID-19 is associated with HCWs compared to students and not with MMR vaccination.

Our findings did not support the protective effect of MMR; however, larger studies are ongoing to verify this protective effect [18]. Lundberg et al. [19] analyzed recent MMR vaccination (up to 2.5 years prior) and found a protective effect only for men (OR = 0.43; 95%CI 0.24–0.79). The authors did not try to explain this result, but it is well known that males are at a higher risk of developing a severe COVID-19 disease that requires the intensive care unit, so the MMR vaccination effect could be valuable for them, mainly when COVID-19 vaccination is not available.

Regarding the severity of COVID-19, the overall students presented mild symptoms involving only upper respiratory symptoms and loss of smell and taste, while in hospital workers, 10% of subjects reported lower respiratory symptoms and 13 required hospitalization, of which 11 were not vaccinated with MMR vaccine. This finding suggests that immunity induced through MMR vaccination could play a positive role in protection against SARS-CoV-2 infection. Mysore [20] demonstrated that pre-existing memory T cells, specific for antigens in previously administered MMR, were reactivated by SARS CoV-2 antigens following COVID 19 or COVID-19 vaccination. Memory T-cells have been implicated in antiviral immunity. These authors found that prior MMR vaccination was associated with reduced disease severity and mortality in the COVID-19 patient cohort. Marakasova et al. [21] suggested that the protective effect could be related to measles protein homology with SARS-CoV-2 that might contribute to cross-reactivity or complement activation protection in vaccinated subjects and not in wild-type disease.

Our study has some limitations. We analyzed workers and students routinely screened for SARS-CoV2 infection, and the prevalence of infection was higher than that reported for the general population. For the same reason, symptoms reported were generally mild, and positive surveillance permitted the identification of all COVID-19 cases.

The strengths of our study include the large number of workers and medical students involved, the follow-up performed to detect the early signs of COVID-19, the availability of data on MMR vaccination, and antibodies against measles, mumps, and rubella.

In conclusion, our study found a mild, non-statistically relevant reduction of SARS-CoV-2 infections in workers vaccinated with MMR, but the majority (11/13) of healthcare workers who needed hospitalization were not vaccinated for MMR. The possible preventive role of MMR and other vaccines needs to be studied in larger studies because the available evidence suggests a protective role for many recently administered (<5 years) vaccines [12].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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