Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 39 (2021) 4414–4418

Contents lists available at ScienceDirect

Vaccine

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

Short communication

Recent MMR vaccination in health care workers and Covid-19: A test negative case-control study

Lisa Lundberg [a], Maria Bygdell [b], Gustaf Stukat von Feilitzen [c], Susanne Woxenius [d], Claes Ohlsson [b], Jenny M. Kindblom [b,e], Susannah Leach [a,f,*]

[a] Dept. of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden
[b] Centre for Bone and Arthritis Research, Dept. of Internal Medicine and Clinical Nutrition, Inst. of Medicine, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[c] Dept. of Medical Microbiology, Sahlgrenska University Hospital, Gothenburg, Sweden
[d] Dept. of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden
[e] Pediatric Clinical Research Center, Sahlgrenska University Hospital, Gothenburg, Sweden
[f] University of Gothenburg Vaccine Research Institute (GUVAX), Dept. of Microbiology and Immunology, Inst. of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 10 April 2021
Received in revised form 14 June 2021
Accepted 18 June 2021
Available online 22 June 2021

Keywords:
SARS-CoV-2
Covid-19
MMR vaccine

ABSTRACT

Background: It has been hypothesised that the measles-mumps-rubella (MMR) vaccine may afford cross-protection against SARS-CoV-2 which may contribute to the wide variability in disease severity of Covid-19.
Methods: We employed a test negative case-control study, utilising a recent measles outbreak during which many healthcare workers received the MMR vaccine, to investigate the potential protective effect of MMR against SARS-CoV-2 in 5905 subjects (n = 805 males, n = 5100 females).
Results: The odds ratio for testing positive for SARS-CoV-2, in recently MMR-vaccinated compared to not recently MMR-vaccinated individuals was 0.91 (95% CI 0.76, 1.09). An interaction analysis showed a significant interaction for sex. After sex-stratification, the odds ratio for testing positive for males was 0.43 (95% CI 0.24, 0.79, P = 0.006), and 1.01 (95% CI 0.83, 1.22, P = 0.92) for females.
Conclusion: Our results indicate that there may be a protective effect of the MMR vaccine against SARS-CoV-2 in males but not females.

1. Introduction

A hallmark of Covid-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the wide variability in disease severity, from asymptomatic infection to severe respiratory failure and death [1]. Even though a number of risk factors for severe infection have been identified, such as old age, male sex and elevated BMI, it is still incompletely understood why some individuals become so severely affected. The fact that children under the age of 10 appear more protected against severe disease has given rise to many hypotheses, such as age-related differences in distribution and affinity of the viral receptor angiotensin converting enzyme 2 receptors, or pre-existing immunity to coronaviruses [2]. It has also been postulated that childhood vaccinations against other infections can be of importance, supported by reports indicating that live attenuated vaccines may confer protection against non-targeted pathogens [3]. Furthermore, amino acid sequence homologies have been found between the SARS-CoV-2 and measles, rubella and mumps viruses [4,5], and a recent study showed a significant inverse correlation between mumps IgG titres and Covid-19 severity in individuals who had received the measles-mumps-rubella (MMR) vaccine in childhood [6]. There have also been early reports regarding populations with recent MMR vaccination, in whom Covid-19 infections appear less severe or the mortality rate has been lower [7].

A placebo-controlled randomised clinical trial of 30 000 subjects is presently recruiting to study the protective effect of MMR vaccination against laboratory test-confirmed symptomatic Covid-19 [8]. Pending these trial results, we utilised a recent measles outbreak in 2018, during which many health care workers (HCW) received the MMR vaccine. We employed a test negative case-control study, considered suitable for estimating vaccine effectiveness [9] and recently used in several Covid-19 vaccine studies [10,11], to investigate whether recent MMR vaccination

* Corresponding author: University of Gothenburg, Dept. of Microbiology and Immunology, Box 435, 40530, Gothenburg, Sweden.
E-mail address: susannah.leach@microbio.gu.se (S. Leach).

https://doi.org/10.1016/j.vaccine.2021.06.045
0264-410X/

may protect against SARS-CoV-2 and/or the development of severe Covid-19.

2. Methods

2.1. Exposure

A measles outbreak in 2018 in Gothenburg, Sweden, made it apparent that immunity against measles, defined as having had measles or having received two doses of measles-containing vaccine, was heterogeneous among HCW, especially those born between 1960 and 1981. Those born before 1960 are assumed to have been infected by measles, and MMR coverage in those born in 1982 and later is very high. The single-antigen measles vaccine was introduced in Sweden in 1971, but the implementation was incomplete and it was replaced by the MMR vaccine in 1982. Data from before 1970 is lacking, but approximately 89% of those born in 1970 are believed to have received at least one dose of measles-containing vaccine, with this coverage increasing to and remaining above 90% for those born 1972 and after [12]. All HCW employed by the Region Västra Götaland were thus required to review their vaccination status and MMR vaccine was offered free of charge via the workplace to all who were not considered immune.

2.2. Outcome

During the Covid-19 pandemic, all HCW experiencing symptoms indicative of Covid-19 (e.g., fever, dry cough, upper respiratory tract symptoms) have been offered PCR-testing for SARS-CoV-2 via the workplace, starting in March 2020 with prioritised units (intensive care, infectious diseases, transplant surgery etc.) and thereafter continuously expanding to include HCW in all areas. Serology testing for prior SARS-CoV-2 infection became available to HCW in late May 2020, to test for past infection, including in those who had been unable to access a PCR test in the early phases of the pandemic. Studies have shown that the vast majority of SARS-CoV-2 infected individuals seroconvert [13,14]. Nasal swabs were qualitatively analysed using the cobas 6800 PCR system (Roche) or using a validated in-house assay (5.2% of samples). Serum samples were screened for nucleocapsid-specific antibodies using the qualitative Architect system (Abbott) and positive samples were confirmed with the quantative iFlash 1800 (YHLO).

The study population thus consisted of HCW (in hospitals and primary care, as well as administrative personnel, laboratory technicians, cleaners etc.) employed by the region born in 1960–1981 and who had been tested for SARS-CoV-2 via the workplace (PCR and/or serology with the appropriate laboratory code). To be eligible for participation, the HCW had to have been working within the region since the measles outbreak in 2018.

Approval was obtained from the Swedish Ethical Review Authority (Registration number 2020–05168). Data extraction of SARS-CoV-2 tests belonging to HCW was performed on the 5th of October 2020. Eligible subjects were contacted twice during a three-week period (starting on the 23rd of October 2020) via their work email for inclusion, and written informed consent was obtained from all participants before engaging in any study-related activities. An electronic questionnaire was sent to the participants containing questions regarding MMR vaccination in 2018 or later, SARS-CoV-2 PCR and/or serology test results, the severity of Covid-19 infection graded on a five-point scale (1: asymptomatic; 2: managed symptoms at home without any assistance; 3: managed symptoms at home but required assistance for activities of daily life; 4: hospitalised, medical ward; 5: hospitalised, intensive care ward), and comorbidities believed to increase the risk of severe Covid-19 (hypertension, cardiovascular disease, chronic kidney disease, type 1/2 diabetes mellitus, chronic obstructive pulmonary disease, immunodeficiency, malignancy, and obesity (BMI $\geq$ 30)).

2.3. Statistical analyses

Differences between the test-positive and test-negative groups, and recently and not-recently MMR-vaccinated groups, were tested using Fischer's exact test for dichotomous variables and student *t* test for continuous variables. Logistic regression was used to estimate the odds of testing positive for SARS-CoV-2 or developing severe Covid-19 (severity 4–5) in subjects receiving MMR vaccine in 2018 or later compared to those who had not. Possible interactions were assessed by addition of an interaction term in the logistic regression models, and $P < 0.05$ for the interaction term was interpreted as statistically significant. The interaction term included the two parameters of interest multiplied by each other. The results are presented as odds ratios with a 95% confidence interval (CI). Age, sex, BMI $\geq$ 30 and the presence of one or more of the above-mentioned comorbidities were considered possible confounders for testing positive and disease severity, and were included as covariates in the adjusted logistic regression models. All statistical analyses were performed using SPSS (version 27).

3. Results

The survey was sent to 12 940 eligible HCW, of which 5905 (45.6%) responded and gave consent to participate. The demography, vaccination status, SARS-CoV-2 test status, Covid-19 details and prevalence of important risk factors of respondents are presented in Table 1.

In total, 756 HCW (12.8%) responded that they had tested positive by PCR and/or serology. Test positivity differed significantly between the sexes (12.4% of women and 15.3% of men, P = 0.03), and in subjects with a BMI over and under 30 (12.4% of subjects < 30 and 15.3% of subjects $\geq$ 30, P = 0.02). Lab records confirming the stated test-positivity were unavailable for 73 (10%) subjects, interpreted as the positive test result was attained outside of the HCW-testing and were thus included.

Of the 1409 HCW reporting recent MMR vaccination, 990 (70.3%) had received one dose, 227 (16.1%) two doses, and 192 (13.6%) could not recall how many doses they had received. The rate of recent MMR-vaccination was higher for women than men (24.5% compared to 19.9%, P = 0.004). Of those recently vaccinated, there was no significant difference in the number of doses administered between women and men (P = 0.81). When considering the number of MMR doses given to subjects born 1960–1970 and 1971–1981, a significantly larger proportion of vaccinated subjects born in the earlier period had received two doses than one (28.2% compared to 10.9%, P < 0.0001; no significant differences between the sexes).

The odds ratio for testing positive for SARS-CoV-2 in recently MMR-vaccinated compared to not recently MMR-vaccinated subjects was 0.91 (95% CI 0.76, 1.09) (Table 2). Adjustment for age, sex, BMI $\geq$ 30 and one or more comorbidities did not alter the results. Because of an interaction between sex and recent MMR vaccination (P = 0.008 for the interaction term recent MMR vaccination $\times$ sex), sex-stratified analyses were also performed. The OR for testing positive in recently vaccinated compared to not recently vaccinated females was not significant, but was significant for males: OR 0.43 (95% CI 0.24, 0.79, P = 0.006). Adjustment for age, BMI $\geq$ 30 and one or more comorbidities did not effect these ORs.

Table 1
Descriptive statistics. Values are numbers (%) unless stated otherwise.

	Total (n = 5905)	**Positive test result**[1] (n = 756)	**Negative test result** (n = 5149)
Recently MMR-vaccinated[2]			
Total	1409	169 (12.0)	1240 (88.0)
Age, median (IQR)[3]	48 (43–53)	47 (43–52)	48 (43–53)
Sex			
Male	160	13 (8.1)	147 (91.9)[4]
Female	1249	156 (12.5)	1093 (87.5)
BMI[5]			
<30	1173	138 (11.8)	1035 (88.2)[6]
≥30	229	31 (13.5)	198 (86.5)
Comorbidity[7]			
≥ 1	220	24 (10.9)	196 (89.1)
None	1189	145 (12.2)	1044 (87.8)
Number of days of symptoms, median (IQR)[8]	–	14 (7–21)	–
Severity[9]			
1-3	–	166 (98.2)	–
4-5	–	3 (1.8)	–
Most recent MMR vaccine dose, year			
2018	985	116	869
2019	116	16	100
2020	25	2	23
Unknown	283	35	248
Not recently MMR-vaccinated			
Total	4496	587 (13.1)	3909 (86.9)
Age median (IQR)[3]	50 (44–55)	50 (45–55)	50 (44–55)
Sex			
Male	645	110 (17.1)	535 (82.9)[4]
Female	3851	477 (12.4)	3374 (87.6)
BMI[5]			
<30	3776	475 (12.6)	3301 (87.4)[6]
≥30	691	110 (15.9)	581 (84.1)
Comorbidity[7]			
≥ 1	840	100 (11.9)	740 (88.1)
None	3656	487 (13.3)	3169 (86.7)
Number of days of symptoms, median (IQR)[8]	–	14 (7–20)	–
Severity[9]			
1-3	–	573 (97.6)	–
4-5	–	14 (2.4)	–

[1] SARS-CoV-2 positivity by PCR in 13%, serology in 49%, both in 28% and unknown 10%.
[2] MMR (measles-mumps-rubella) vaccine.
[3] Age on the 1st of January 2020, IQR: interquartile range.
[4] Difference in sexes in positive and negative test groups, P = 0.027.
[5] BMI: body mass index (n = 5869).
[6] Difference in BMI ≥ 30 in positive and negative test groups, P = 0.016.
[7] Comorbidities, excluding BMI ≥ 30: hypertension, cardiovascular disease, chronic kidney disease, type 1/2 diabetes mellitus, chronic obstructive pulmonary disease, immunodeficiency, malignancy.
[8] Number of sick days due to Covid-19 (n = 728).
[9] Severity 1–3: no hospital admission. Severity 4–5: hospital admission.

Table 2
Odds ratios for testing positive for SARS-CoV-2.

		Odds ratio (95% CI)	**Adjusted odds ratio**[1] **(95% CI)**
Not recently MMR-vaccinated		Base	Base
Recently MMR-vaccinated[2]		0.91 (0.76–1.09)	0.91 (0.76–1.10)
Stratification for			
Sex	Female	1.01 (0.83–1.23)	1.01 (0.83–1.22)
	Male	0.43 (0.24–0.79)[3]	0.44 (0.24–0.80)[4]
Age	1960–1970	0.81 (0.62–1.06)	0.81 (0.62–1.06)
	1971–1981	1.01 (0.79–1.30)	1.02 (0.79–1.31)

[1] Adjusted for age, sex, BMI ≥ 30, ≥1 comorbidity: hypertension, cardiovascular disease, chronic kidney disease, type 1/2 diabetes mellitus, chronic obstructive pulmonary disease, immunodeficiency, malignancy. Stratified analyses not adjusted for factor of stratification.
[2] MMR-vaccinated in 2018–2020.
[3] P = 0.006.
[4] P = 0.008.

No interaction was seen between age and recent MMR vaccination (P = 0.26). However, because a higher proportion of subjects born before 1970 recently had received two MMR doses than those born later, analyses were also stratified by age (Table 2). The ORs were not statistically significant for either age group, and the confidence intervals overlapped with a wide margin. When considering if more doses could afford a higher level of protection, the OR for testing positive was 0.92 (95% CI 0.75,1.13) for one dose and

0.79 (95 %CI 0.50, 1.19) for two doses, excluding subjects who could not recall how many doses they had received. When only considering males, the ORs were 0.54 (95% CI 0.27, 1.07) for one dose (n = 100) and 0.21 (95% CI 0.03, 1.58) for two doses (n = 24).

The severity of Covid-19 among recently vaccinated and not are shown in Table 1. Fourteen not recently vaccinated subjects had required hospitalisation (severity group 4–5, 2.4%) compared to only three recently vaccinated subjects (1.8%), making the OR for hospital admission 0.74 (95% CI 0.21, 2.60). After adjusting for age, sex, BMI $\geq$ 30 and the prevalence of one or more comorbidities, the adjusted OR for hospital admission was 0.94 (95% CI 0.26, 3.46).

In sensitivity analyses, exclusion of subjects whose test-positivity could not be confirmed in the lab records did not change conclusions based on statistical significance levels (data not shown). Similarily, when considering subjects vaccinated in 2019 or 2020 (n = 141) and subjects vaccinated only 2018 (n = 985) separately, results remained largely unchanged, with odds ratios of 0.95 (95% CI 0.56, 1.52) and 0.89 (95% CI 0.72, 1.10) respectively.

4. Discussion

The concept that existing vaccines may afford protection against heterologous pathogens is particularly appealing in pandemic situations, and the potential of MMR vaccine protecting against Covid-19 has been considered [7,8]. Our results suggest that MMR-vaccination up to 2.5 years prior affords no substantial protective effect against SARS-CoV-2 infection when considering the whole study population. However, in sex-stratified analyses, there was a significantly reduced risk of testing positive in recently MMR-vaccinated men, equating to an estimated 57% vaccine effectiveness at preventing symptomatic disease (P = 0.006).

A *meta*-analysis of more than three million cases of COVID-19 have shown that the proportions of COVID-19 cases are similar between the sexes, but males are approximately three times more likely to require intensive care [15]. Simultaneously, females usually develop greater immune responses to vaccination than males [16], though this does not necessarily have to translate to higher protection. It could be argued that factors specific for females mask potential protective effects of MMR-vaccination, such as higher levels of adult vaccination (due to screening for rubella-antibodies in conjunction with pregnancy). However, there were no statistically significant differences between the sexes regarding the number of doses administered during the 2018 measles outbreak, indicating that women in this age group had not had more vaccine doses during childhood or adulthood than men. Whilst the protective effectiveness seen in men in this study is interesting, the result is based on few subjects (n = 805) and it cannot be ruled out that it may be due to residual confounding.

There was no indication that more recent MMR vaccination (vaccinated in 2020 or 2019 compared to in 2018) afforded higher protection from symptomatic infection, but there was a tendency that two doses may have afforded higher protection compared to one. The low number of subjects developing severe Covid-19 in our population makes drawing any conclusions about the potential of MMR vaccine protecting against severe Covid-19 symptoms difficult. Of note, of the 17 severe Covid-19 cases in this study, all three who had been recently MMR vaccinated were female.

This study has several limitations. The study population is of a specific age group, and has an excess of females which, whilst representative of HCW, does not reflect the general population. Whilst we believe that by considering both PCR and serology results, the testing can be considered comprehensive of the first wave of infection, as information regarding numbers of symptomatic HCW and proportions tested is lacking, we do not have the opportunity to completely assess this. By using work email, the possibility that some HCW missed the study invitation because of long-term sick leave due to Covid-19 cannot be excluded, which could be a source of bias. Data regarding occupation type and level of exposure to Covid-19 patients is also lacking. A questionnaire had to be used to gather data, as vaccinations are unavailable from the electronic medical journal system used in the county. It is thus possible that MMR vaccination was subjected to recall bias, though considering MMR vaccine was administered maximumly 2.5 years before this study, this is unlikely. It is also possible that the SARS-CoV-2-negative group contains some false negatives due to delayed PCR-testing or absence of seroconversion. However, these would likely be evenly distributed between the recently MMR-vaccinated and not recently MMR-vaccinated groups and thus there would be little bias towards the null-value due to non-differential misclassification of outcome. Lastly, the observational nature of this study includes risk of unknown bias and confounding.

In conclusion, we performed a test negative case-control study using a recent measles outbreak with MMR vaccination in HCW to investigate the potential protective effect of MMR vaccine against SARS-CoV-2 and severe Covid-19. Whilst our results do not support a substantial protective effect of the MMR vaccine in the whole study population, a significant effectiveness of approximatly 57% at preventing symptomatic disease was seen in men. However, it cannot be excluded that these results are due to residual confounding. Despite the fact that antigen-specific vaccines against SARS-CoV-2 are now available, they are far from universally accessible and the potential global health gains of non-specific disease-modifying immunisations are vast. It will be very interesting to see the results from the planned RCT on the protective effects of MMR vaccination against Covid-19, and the present study emphasizes that it may be important to perform sex-stratified analyses.

Funding

This work was supported by the Swedish State Support for Clinical Research (https://www.alfvastragotaland.se, ALFGBG-679621 (SL)). The diagnostic work that led to the generation of these results was funded by the Swedish state.

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.

Acknowledgements

We thank Jari Martikainen, Bioinformatics Core Facility, Sahlgrenska Academy, University of Gothenburg, for support with the statistical analyses.

References

[1] Samadizadeh S, Masoudi M, Rastegar M, Salimi V, Shahbaz MB, Tahamtan A. COVID-19: Why does disease severity vary among individuals?. Respir Med. 2021;180:106356.
[2] Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Child. 2020.
[3] Aaby P, Benn CS. Developing the concept of beneficial non-specific effect of live vaccines with epidemiological studies. Clin Microbiol Infect. 2019;25(12):1459–67.
[4] Sidiq KR, Sabir DK, Ali SM, Kodzius R. Does Early Childhood Vaccination Protect Against COVID-19? Front Mol Biosci. Frontiers Media S.A. 2020;7:120. 120.
[5] Young A, Neumann B, Mendez RF, et al. 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;:2020.04.10.20053207.

[6] Gold JE, Baumgartl WH, Okyay RA, et al. Analysis of Measles-Mumps-Rubella (MMR) Titers of Recovered COVID-19 Patients. Pirofski L, editor. mBio. 2020; 11(6):e02628-20.
[7] Ashford JW, Gold JE, Huenergardt MA, et al. MMR Vaccination: A Potential Strategy to Reduce Severity and Mortality of COVID-19 Illness. Am J Med. 2020/10/23 ed. Excerpta Medica; 2021; 134(2):153–155.
[8] Avidan M. An International, Multi-site, Bayesian Platform Adaptive, Randomized, Placebo-controlled Trial Assessing the Effectiveness of Candidate Agents in Mitigating COVID-19 Disease in Adults [Internet]. clinicaltrials.gov; 2021 Mar. Report No.: NCT04333732. Available from: https://clinicaltrials.gov/ct2/show/NCT04333732
[9] De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro Surveill. Sweden 2013;18(37).
[10] Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021;373:n1088.
[11] Hyams C, Marlow R, Maseko Z, et al. Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. Pre-print. 2021. Available from: https://papers.ssrn.com/abstract=3796835
[12] Vaccination coverage - measles, mumps and rubella. [Internet]. Public Health Agency of Sweden. [cited 2021 Jun 8]. Available from: http://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/vaccinationsstatistik/figurer-vaccinationstackning/
[13] Long Q-X, Liu B-Z, Deng H-J, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. Nature Publishing Group; 2020; 26(6):845–848.
[14] Marklund E, Leach S, Axelsson H, et al. Serum-IgG responses to SARS-CoV-2 after mild and severe COVID-19 infection and analysis of IgG non-responders. PLoS ONE 2020;15(10):e0241104.
[15] Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11(1):6317.
[16] Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg. 2015;109(1):9–15.