Outcomes of the COVID-19 infection in people previously vaccinated against influenza: a population-based cohort study with primary health care electronic records.

Maria Giner-Soriano, Vanessa de Dios, Dan Ouchi, Carles Vilaplana-Carnerero, Mònica Monteagudo, Rosa Morros

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Maria Giner-Soriano[1, 2*] PharmD, PhD; Vanessa de Dios[3*] MD; Dan Ouchi[1, 2*] MSc; Carles Vilaplana-Carnerero[1, 2*] PharmD, PhD; Mònica Monteagudo[1, 2*] MD, PhD; Rosa Morros[1, 2, 4, 5*] MD, PhD

[1]Universitat Autònoma de Barcelona Bellaterra (Cerdanyola del Vallès) ES

[2]Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain. Barcelona ES

[3]Department of Clinical Pharmacology, Medicines Area, Hospital Clinic of Barcelona, Barcelona, Spain Barcelona ES

[4]Plataforma SCReN, UICEC IDIAPJGol, Barcelona, Spain Barcelona ES

[5]Institut Català de la Salut Barcelona ES

[*]these authors contributed equally

Corresponding Author:
Maria Giner-Soriano PharmD, PhD
Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.
Gran Via de les Corts Catalanes 587, àtic
Barcelona
ES

Abstract

Background: A possible link between influenza immunization and susceptibility to COVID-19 infection has been previously suggested due to a boost in the immunity against SARS-CoV-2.

Objective: We aimed to assess this hypothetic association in our setting.

Methods: Population-based cohort study including all patients with COVID-19 registers in the primary health care (PHC) electronic records during the first wave of the COVID-19 pandemic (1st March 2020 – 30th June 2020) in Catalonia, Spain. We compared those people ever exposed to influenza vaccine before the COVID-19 infection with those never exposed. The data source is SIDIAP, capturing PHC information of 5.8 million people from Catalonia. The main outcomes assessed during follow-up were diagnosis of pneumonia, hospital admission and mortality.

Results: We included 309,039 COVID-19 patients and compared them according to their influenza immunization status, being 114,181 (36.9%) vaccinated at least once and 194,858 (63.1%) never vaccinated. 21,721 (19%) of the flu-vaccinated and 11,000 (5.7%) of the non-vaccinated had at least one of the outcomes assessed. Those vaccinated against flu at any time, recently or recurrently before COVID-19 had higher risk of presenting at least one of the outcomes than those non-vaccinated. When we excluded people living in long-term care facilities, the results were similar.

Conclusions: We were not able to find a protective role of the immunity conferred by the influenza vaccine on the outcomes of the COVID-19 infection, as the risk of COVID-19 complications was higher in the vaccinated than in the non-vaccinated. Our results are from the first wave of the pandemic, were more complications and mortality due to COVID-19 occurred. Despite that, our study adds more evidence to the analysis of the possible link between the quality of the immunity and the COVID-19 outcomes and to the analysis of PHC patients. Clinical Trial: AEMPS classification
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Maria Giner-Soriano[1,2], Vanessa de Dios[3], Dan Ouchi[1,2], Carles Vilaplana-Carnerero[1,2], Mònica Monteagudo[1,2], Rosa Morros[1,2,4,5]

1 Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.
2 Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.
3 Department of Clinical Pharmacology, Medicines Area, Hospital Clinic of Barcelona, Barcelona, Spain.
4 Plataforma SCReN, UICEC IDIAPJGol, Barcelona, Spain.
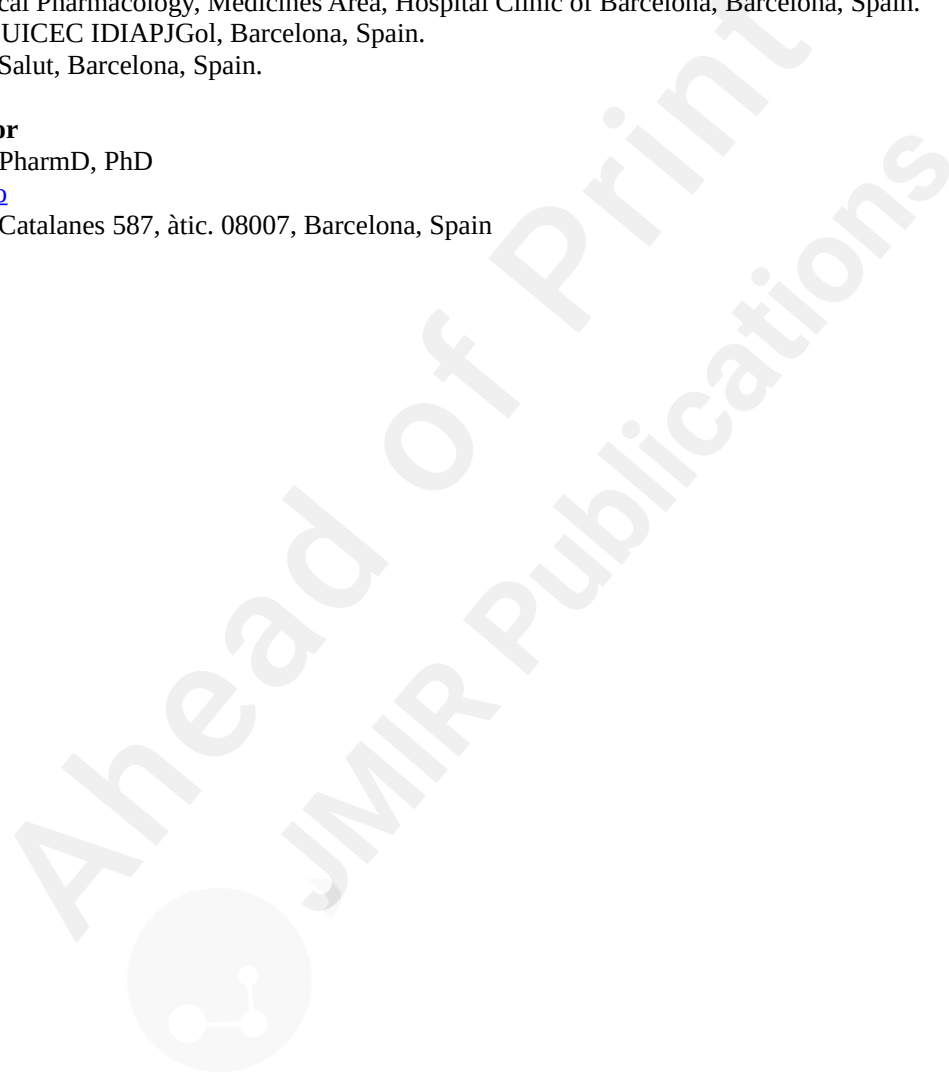5 Institut Català de la Salut, Barcelona, Spain.

Corresponding author
Maria Giner-Soriano, PharmD, PhD
mginer@idiapjgol.info
Gran Via de les Corts Catalanes 587, àtic. 08007, Barcelona, Spain
+34 934 824 110

Abstract

Background

A possible link between influenza immunization and susceptibility to complications of the COVID-19 infection has been previously suggested due to a boost in the immunity against SARS-CoV-2. We hypothesized that the immunity resulting from the previous influenza vaccination would boost part of the immunity against SARS-CoV-2 and aimed to analyze if COVID-19 patients could have benefited from vaccination against influenza.

Methods

Population-based cohort study including all patients with COVID-19 registers in the primary health care (PHC) electronic records during the first wave of the COVID-19 pandemic (1st March 2020 – 30th June 2020) in Catalonia, Spain. We compared those people ever exposed to influenza vaccine before the COVID-19 infection with those never exposed. The data source is SIDIAP (Information System for Research in Primary Care), capturing PHC information of 5.8 million people from Catalonia. The main outcomes assessed during follow-up were diagnosis of pneumonia, hospital admission and mortality.

Results

We included 309,039 COVID-19 patients and compared them according to their influenza immunization status, being 114,181 (36.9%) vaccinated at least once and 194,858 (63.1%) never vaccinated. 21,721 (19%) of the flu-vaccinated and 11,000 (5.7%) of the non-vaccinated had at least one of the outcomes assessed. Those vaccinated against flu at any time (OR 1.14, 95% CI 1.10-1.19), recently (OR 1.13, 95% CI 1.10-1.18) or recurrently (OR 1.10, 95% CI 1.05-1.15) before COVID-19 had higher risk of presenting at least one of the outcomes than those non-vaccinated. When we excluded people living in long-term care facilities, the results were similar.

Conclusions

We were not able to find a protective role of the immunity conferred by the influenza vaccine on the outcomes of the COVID-19 infection, as the risk of COVID-19 complications was higher in the vaccinated than in the non-vaccinated. Our results correspond to the first wave of the pandemic, where more complications and mortality due to COVID-19 occurred. Despite that, our study adds more evidence to the analysis of the possible link between the quality of the immunity and the COVID-19 outcomes, particularly in the PHC setting.

Keywords

SARS-CoV2; COVID-19; influenza vaccines; pneumonia; electronic health records; primary health care.

AEMPS classification

IDI-VAC-2020-21. *Estudio Posautorización con Otros Diseños diferentes al de seguimiento prospectivo*, EPA-OD. 15th September 2020.

Introduction

The severe acute respiratory syndrome-2 (SARS-CoV-2) is caused by a novel coronavirus emerged in China in 2019, becoming the primary agent of a new pandemic which was rapidly spread worldwide, causing the coronavirus disease, COVID-19,[1] with an average global infection fatality rate of around 0.15%, depending on the data analyzed.[2] This coronavirus mainly affects the respiratory tract, and uses surface proteins in order to infect the host.[3]

Although new variants of SARS-CoV-2 have emerged since December 2020, the coronavirus' genome is composed by RNA and depends on the RNA polymerase to generate its proteins, with a mechanism of error correction that results in a lower mutation rate in comparison with the influenza virus.[4] This low mutation rate may suggest that the vaccines developed against SARS-CoV-2, as well as the immunity generated in those patients who were infected, could represent a long-lasting immunity.[5,6]

COVID-19, as influenza A and B, are caused by RNA virus and produce similar symptoms. The influenza virus needs the hemagglutinin and neuraminidase surface proteins to infect, whereas SARS-CoV-2 needs S protein.[5] Previous in vitro and animal studies suggest an induction pathway of indirect etiological immunity between the flu vaccine and the COVID-19. Animal models suggest that some influenza subtypes might lead to a regulation of the angiotensin-converting enzyme-2 (ACE2), with protecting properties against SARS.[7] An unspecific effect of infection and vaccination on the immune system and susceptibility to other infections has also been reported, although with discordant data.[8–10] Some modelling studies have suggested a possible association between influenza immunization and COVID-19.[11–14]

A study conducted in Australia assessed the cellular and humoral immune responses during and after the disease in a patient with mild COVID-19 infection. They found that immune response in different cell types was associated with clinical recovery. These results are coincident with similar findings in influenza patients reported by the same authors.[15,16]

Other authors observed different susceptibility to COVID-19 in children of different ages with a lower infection rate than adults and elderly.[17] Although the mechanism of these differences in severity and susceptibility is unclear, a possible explanation might be the difference in the quantity and quality of the immune function determined by the history of infections and/or the recent vaccines administered.[18]

Consequently, a link between the quality of the immunity and the COVID-19 recovery may exist. Thus, we hypothesized that the immunity resulting from the previous influenza vaccination would boost part of the immunity against SARS-CoV-2 and aimed to analyze if COVID-19 patients could have benefited from vaccination against influenza.

Methods

Study design

Population-based cohort study including all adult patients with COVID-19 infection in Catalonia, Spain , registered as confirmed (by polymerase chain reaction, PCR) or as probable (not confirmed by PCR but with ICD-10 codes registered compatible with COVID-19 infection) in the primary health care (PHC). All COVID-19 patients were diagnosed from the pandemic's onset (March 2020) to June 30th 2020. Patients were compared according to the influenza vaccination status between those ever exposed to influenza vaccine before the COVID-19 infection (vaccinated in the previous influenza seasonal campaign, 2019-2020, or before)[19] with those non-exposed.

Data source

The study data source is the Information System for Research in Primary Care (SIDIAP),[20] which captures clinical information of approximately 5.8 million people from Catalonia, Spain (around 80% of the Catalan population). This information is pseudonymized, originated from different data sources: 1) ECAP (electronic health records in PHC of the Catalan Health Institute); including socio-demographic characteristics, residents in nursing homes/long-term facilities, comorbidities registered as International Classification of Diseases (ICD)-10 codes,[21] specialist referrals, clinical parameters, toxic habits, sickness leave, date of death, laboratory test data, and drug prescriptions issued in PHC, registered as for the anatomical therapeutic chemical classification system (ATC); [22] 2) pharmacy invoice data corresponding to the PHC drug prescriptions; 3) database of diagnoses at hospital discharge[23] and 4) COVID-19 data from the Catalan Agency of Health Quality and Evaluation (AQuAS).[24]

COVID-19 classification

Subjects were classified according to the following criteria: *confirmed cases* are those with a confirmed COVID-19 diagnostic record, PCR+ and/or a positive serology test. Those with a non-confirmed diagnosis or test (possible or unclear) along with any individual with a record of hospitalization, pneumonia and/or death related to COVID-19 were considered *possible cases*. During the first wave of the COVID-19 pandemic in Catalonia, PCR tests were not routinely conducted to all patients with compatible symptoms, due to the unavailability of laboratory kits to do the tests. Thus, we needed to capture those patients with possible diagnosis of COVID-19, such as those admitted to hospital with pneumonia or other COVID-19 symptoms who were not tested. We designed an algorithm to classify patients as "COVID possible" when there was not a test result available combining the registers proceeding from different databases: PCR tests or serology tests conducted in different settings, discharge diagnoses of pneumonia from Catalan hospitals or from Emergency Departments, and ICD-10 diagnoses related with COVID-19 coded in PHC. The date of COVID-19 diagnosis was set to be the first of all records used per patient. To guarantee that our algorithm is not far from the Catalan population, the resulting cohort was compared to the official COVID-19 cases provided by the AQuAS during the pandemic.[24]

Exposure to influenza vaccine

Patients were classified as exposed to influenza vaccine if they had been vaccinated at any time before the COVID-19 infection, and grouped according to the seasonal vaccination campaign: immediately previous campaign (2019-2020) and/or other vaccination campaigns (2018-2019 and before).[19,25]

Variables

At baseline, the variables captured were: sex, age, geographical area, MEDEA socioeconomic index (deprivation index based on five indicators of socio-economic position. The higher this is, the worse the deprivation is, and it allows analyzing health inequalities),[26] body mass index (BMI), residence in nursing homes, smoking habit, comorbidities, exposure to influenza vaccines and pneumococcal and tuberculosis vaccines.

The main outcomes assessed during follow-up (up to June 2020) were at least one of the following variables: diagnosis of pneumonia, hospital admission, and mortality. The risk of these events was analyzed in those people who had been vaccinated against influenza at any time before COVID-19 infection, in those recently vaccinated (campaign 2019-2020) and in those systematically vaccinated (who had been vaccinated at least during three different campaigns). We analyzed the same outcomes excluding those people living in long-term care facilities (LTCF), where the vaccination is nearly universal in our country.[27]

Statistical analysis

Quantitative variables were described as the mean and standard deviation, whereas categorical variables were described as the proportion over the exposed and non-exposed individuals. Univariate analyses were based on Student's t-test or Chi-square test depending on the variable.

For each outcome, we fitted a logistic regression model to estimate an odds ratio (OR) comparing the prevalence of each outcome among individuals exposed to influenza vaccine to those non-exposed to the vaccine. The logistic model was fitted including other covariables such as smoking habits, age, comorbidities (asthma, autoimmune disorders, prior cerebrovascular disease, chronic kidney disease, chronic pulmonary obstructive disease, diabetes, heart failure, hypertension, ischemic heart disease, mental-behavioral disorders, obesity, organ transplant, other respiratory diseases), concomitant drugs and previous vaccines (pneumococcal and tuberculosis).As a sensitivity analysis, we conducted the same analysis on a matched population. Exposed to flu-vaccine were 1:2 matched to non-vaccinated controls according to age and gender at the time of infection or on index date, and the reported ORs were obtained by fitting a conditional logistic regression model (clogit) accounting for matched pairs and adjusted using the same covariables as in the logistic model. We used the Wald test on the fitted coefficient to determine whether the log-odds was significantly different from zero at a 0.05 level. All analyses were performed in R software (v4.1.0 or above).

Ethical considerations

The study protocol was approved by the Research Ethics Committee of IDIAPJGol (June 3rd 2020). This is a database research study which has been conducted according to the guidelines of the Declaration of Helsinki (Fortaleza, Brazil 2013) and does not require consent from the people included to participate or for publication. The need for consent was waived by the Research Ethics Committee of IDIAPJGol as it is deemed unnecessary according to European legislation (Regulation [EU] 2016/679).

Results

We included 309,039 infected with COVID-19 during the first pandemic's wave according to their influenza immunization status (Table 1, Supplementary Table 1); 114,181 (36.9%) had received the flu vaccine at least once before the COVID-19 infection and 194,858 (63.1%) had not been vaccinated, with more women in both groups, especially in the vaccinated cohort (61% women *vs* 39% men). The mean age was higher for vaccinated (64.3 years-old, 52.3% older than 65). Vaccinated people had more comorbidities than non-vaccinated.

Table 1. Socio-demographic and clinical characteristics of the population included in the study

		Overall	Non-vaccinated against flu	Flu-vaccinated at least once before COVID-19	P-value
N (%)		309039	194858	114181	
COVID-19 status	Confirmed	164557 (53.2)	105788 (54.3)	58769 (51.5)	<.001
	Possible	144482 (46.8)	89070 (45.7)	55412 (48.5)	
Gender	Female	173071 (56.0)	103413 (53.1)	69658 (61.0)	<.001
	Male	135968 (44.0)	91445 (46.9)	44523 (39.0)	
Age, mean (SD)		49.3 (22.3)	40.6 (17.5)	64.3 (21.7)	<.001
	≤40	108950 (35.3)	90894 (46.6)	18056 (15.8)	<.001
	41-65	129576 (41.9)	93116 (47.8)	36460 (31.9)	
	>65	70513 (22.8)	10848 (5.6)	59665 (52.3)	
Smoker		119554 (38.7)	72806 (37.4)	46748 (40.9)	<.001
Obesity		78882 (25.5)	36973 (19.0)	41909 (36.7)	<.001
LTCF resident		28360 (9.2)	3146 (1.6)	25214 (22.1)	<.001
Geographical information (MEDEA)	Unknown	278 (0.1)	201 (0.1)	77 (0.1)	<.001
	Urban	252014 (81.5)	159859 (82.0)	92155 (80.7)	
	Rural	56747 (18.4)	34798 (17.9)	21949 (19.2)	
Comorbidities	Asthma	22734 (7.4)	9029 (4.6)	13705 (12.0)	<.001
	Autoimmune disorders	30783 (10.0)	14005 (7.2)	16778 (14.7)	<.001
	Cancer	23600 (7.6)	6832 (3.5)	16768 (14.7)	<.001
	Cerebrovascular disease	6937 (2.2)	1053 (0.5)	5884 (5.2)	<.001
	Chronic kidney disease	18450 (6.0)	2088 (1.1)	16362 (14.3)	<.001
	COPD	21771 (7.0)	6155 (3.2)	15616 (13.7)	<.001
	Diabetes	30513 (9.9)	5886 (3.0)	24627 (21.6)	<.001
	Heart failure	8307 (2.7)	693 (0.4)	7614 (6.7)	<.001
	Hypertension	75346 (24.4)	21624 (11.1)	53722 (47.0)	<.001
	Ischaemic heart disease	10049 (3.3)	1837 (0.9)	8212 (7.2)	<.001
	Mental-behavioural disorders	9010 (2.9)	685 (0.4)	8325 (7.3)	<.001
	Organ transplant	893 (0.3)	213 (0.1)	680 (0.6)	<.001
	Other respiratory diseases	16476 (5.3)	6407 (3.3)	10069 (8.8)	<.001
Other vaccines	Pneumococcal	78104 (25.3)	17617 (9.0)	60487 (53.0)	<.001

	Tuberculosis	2974 (1.0)	2412 (1.2)	562 (0.5)	<.001

SD: standard deviation. LTFC: long-term care facility. MEDEA: socioeconomic index. COPD: chronic obstructive pulmonary disease.

Of those receiving the flu vaccine, 66,611 (58.3%) had been recently vaccinated (2019-2020) and 75,311 (66%) had been systematically vaccinated against influenza, at least during three different years (Table 2).

Table 2. Exposure to influenza vaccines before COVID-19 infection

	Vaccinated before COVID-19 infection (N=114,181)
Campaign 2019-2020 (recent immunization, %)	66611 (58.3)
Days from vaccination to infection (median [IQR])	146.0 [127.0, 169.0]
Campaign 2018-2019 (%)	60161 (52.7)
Days from vaccination to infection (median [IQR])	515.0 [495.0, 539.0]
Campaign 2017-2018 or before (%)	102235 (89.5)
Days from vaccination to infection (median [IQR])	931.0 [875.0, 2018.0]
Number of campaigns vaccinated before COVID-19 infection (%)	
1 campaign	26786 (23.5)
2 campaigns	12084 (10.6)
≥3 campaigns (recurrent immunization)*	75311 (66.0)
3 campaigns	7931 (6.9)
4-5 campaigns	11146 (9.8)
6-10 campaigns	18945 (16.6)
>10 campaigns	37289 (32.7)

Of the people with COVID-19 infection, 11,000 (5.7%) non-vaccinated and 21,721 (19%) vaccinated against flu presented at least one of the following events: hospital admission, pneumonia or death. For those receiving the flu vaccine at any time before COVID-19, the risks of hospitalization (adjusted OR 1.14, 95% CI 1.10-1.19) and death (OR 1.32, 1.23-1.42) were higher than for non-vaccinated. For the recently vaccinated, the risk was higher for hospitalization (OR 1.16, 1.1-1.23), pneumonia (OR 1.12, 1.02-1.23) and death (OR 1.14, 1.04-1.24). For people with recurrent vaccination, the risk was also higher for the three outcomes than in non-vaccinated (OR 1.07, 1.16 and 1.24, respectively. See Table 3). We have also analyzed the results in a matched population of vaccinated vs. non-vaccinated, finding higher risk of pneumonia and mortality, with an adjusted OR of 1.11 (95% CI 1.01-1.23) and 1.28 (95% CI 1.07-1.53), respectively (see Supplementary Table 2).

Table 3. Logistic regression model of COVID-19 outcomes according to the influenza immunization status
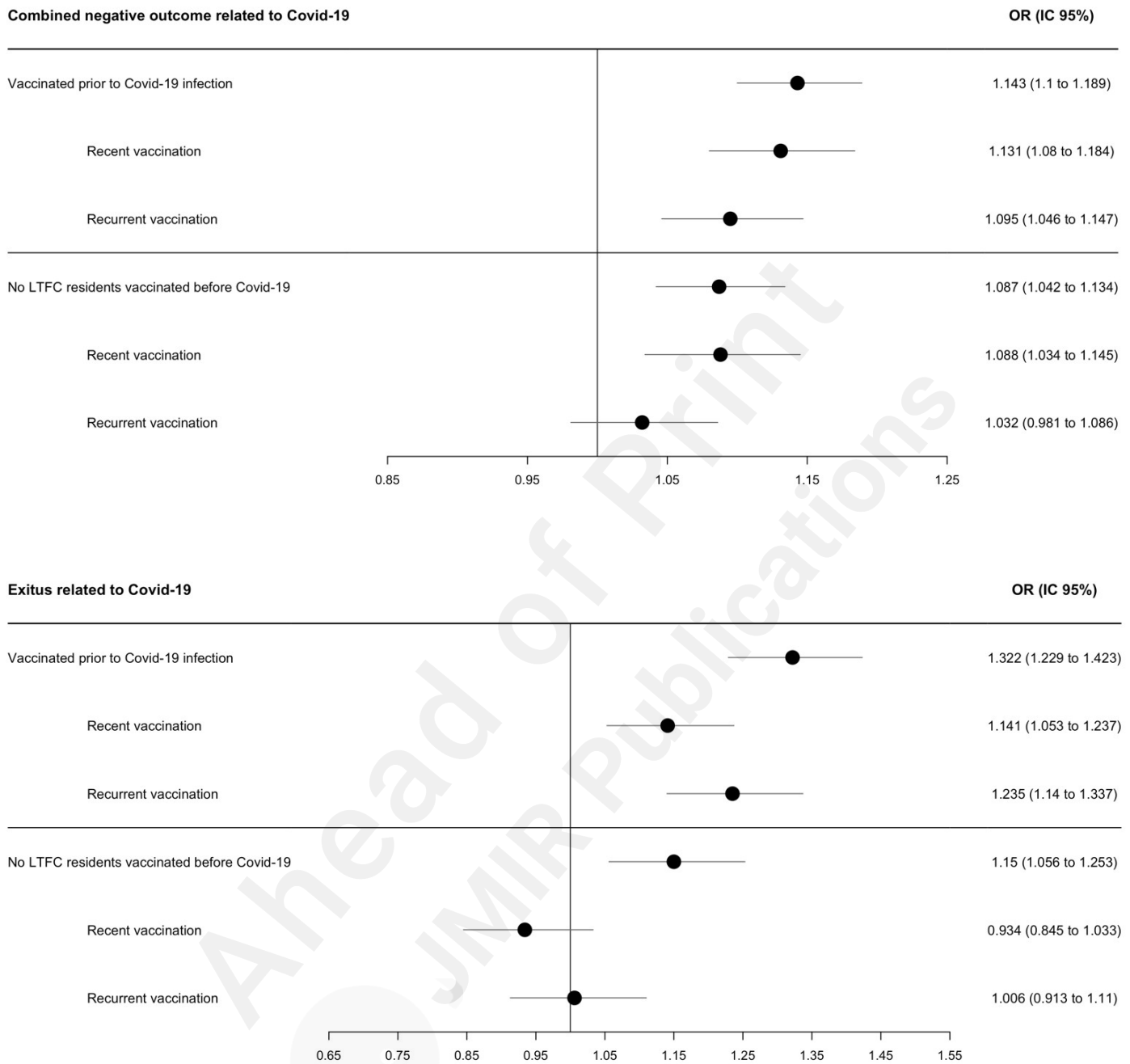
	Influenza immunization status prior to COVID-19 (%)		Multivariable logistic model*	
Any vaccination	**Non-vaccinated (N=194,858)**	**Vaccinated (N=114,181)**	**aOR (95% CI)**	**P-value**

≥1 outcome	11000 (5.7)	21721 (19.0)	1.14 (1.10-1.19)	<.001
Hospitalization	7848 (4.0)	10592 (9.3)	1.10 (1.05-1.15)	<.001
Pneumonia	3011 (1.6)	2740 (2.4)	1.08 (1.00-1.16)	.067
Death	1899 (0.97)	11835 (10.4)	1.32 (1.23-1.42)	<.001
Recent vaccination	**Non-vaccinated (N=194,858)**	**Vaccinated (N=66,611)**	**aOR (95% CI)**	**P-value**
≥1 outcome	11000 (5.7)	15129 (22.7)	1.13 (1.10-1.18)	<.001
Hospitalization	7848 (4.0)	7009 (10.5)	1.16 (1.10-1.23)	<.001
Pneumonia	3011 (1.6)	1731 (2.6)	1.12 (1.02-1.23)	.017
Death	1899 (0.97)	8800 (13.2)	1.14 (1.05-1.24)	.001
Recurrent vaccination	**Non-vaccinated (N=194,858)**	**Vaccinated (N=75,311)**	**aOR (95% CI)**	**P-value**
≥1 outcome	11000 (5.7)	17798 (23.6)	1.10 (1.05-1.15)	<.001
Hospitalization	7848 (4.0)	8122 (10.8)	1.07 (1.02-1.14)	.012
Pneumonia	3011 (1.6)	1942 (2.6)	1.16 (1.06-1.27)	.002
Death	1899 (0.97)	10561 (14.0)	1.24 (1.14-1.34)	<.001

*By fitting a logistic regression model adjusted by relevant covariables: smoking habits, age, comorbidities (asthma, autoimmune disorders, prior cerebrovascular disease, chronic kidney disease, chronic pulmonary obstructive disease, diabetes, heart failure, hypertension, ischaemic heart disease, mental-behavioural disorders, obesity, organ transplant, other respiratory diseases), comedication and previous vaccines (pneumococcal and tuberculosis). aORadj: adjusted odds ratio.

The risks of the outcomes according to the flu-vaccination status and excluding those patients living in LTCF are shown in Figure 1. For non-LTCF residents, the results are similar to those for the whole population, except that there is no increase in mortality although it is non-significant (OR 0.93, 95% CI 0.85-1.03).

Figure 1. Risk of death and of combined COVID-19 complications in all the vaccinated population and excluding people living in long-term care facilities.

Combined negative outcome related to Covid-19   OR (IC 95%)

Vaccinated prior to Covid-19 infection   1.143 (1.1 to 1.189)

Recent vaccination   1.131 (1.08 to 1.184)

Recurrent vaccination   1.095 (1.046 to 1.147)

No LTFC residents vaccinated before Covid-19   1.087 (1.042 to 1.134)

Recent vaccination   1.088 (1.034 to 1.145)

Recurrent vaccination   1.032 (0.981 to 1.086)

0.85   0.95   1.05   1.15   1.25

Exitus related to Covid-19   OR (IC 95%)

Vaccinated prior to Covid-19 infection   1.322 (1.229 to 1.423)

Recent vaccination   1.141 (1.053 to 1.237)

Recurrent vaccination   1.235 (1.14 to 1.337)

No LTFC residents vaccinated before Covid-19   1.15 (1.056 to 1.253)

Recent vaccination   0.934 (0.845 to 1.033)

Recurrent vaccination   1.006 (0.913 to 1.11)

0.65   0.75   0.85   0.95   1.05   1.15   1.25   1.35   1.45   1.55

LTFC: long-term care facilities. OR: odds ratio. IC 95%: 95% confidence interval.
Combined negative outcome includes hospital admission, pneumonia and death.
The first forest plot describes the mortality odds in those vaccinated any time before COVID-19 and in those vaccinated excluding LTFC residents. The second forest plot describes the odds for the combination of outcomes in the vaccinated any time before COVID-19 and in the vaccinated excluding LTFC residents.

Discussion

Principal findings

We analyzed the negative outcomes suffered by people infected by SARS-CoV-2 (n= 309,039), comparing those ever exposed to the influenza immunization with those never vaccinated. Those who received the vaccine any time before having the COVID-19 infection had higher risk of

complications than those non-vaccinated. We found similar results for those recently vaccinated (2019-2020 campaign), and for those systematically vaccinated (at least 3 years), and the same comparisons excluding patients living in LTCF. We also found similar results when matching vaccinated with non-vaccinated individuals. Thus, we did not find a possible link between receiving the flu vaccine and presenting better clinical outcomes of the COVID-19 infection.

Comparison with prior work

Some researchers have studied this possible association. Massoudi and Mohit conducted a study in a hospital in Iran including health-care workers, being 80 of them COVID-19 cases confirmed by PCR or by symptoms, and 181 controls. They concluded that cases were less likely to have received the 2019 vaccine (OR 0.04, 0.01-0.14), suggesting a protective association between influenza vaccine and COVID-19. This study had several limitations, as the lack of availability of COVID-19 test, or the sample limited to the workers of a single hospital.[28]

Candelli et al. studied 602 COVID-19 patients enrolled in the emergency department in a hospital in Italy, 24.9% of them had been previously vaccinated against flu. They found that influenza immunization was independently associated with a lower risk of death at 60 days (OR 0.20, 0.08-0.51), but not with less need of endotracheal intubation (OR 0.73, 0.35-1.56).[29]

A study conducted in Brazil included 92,664 confirmed cases of COVID-19, 31.1% of them had been recently vaccinated against flu. They found that the vaccinated people had a lower risk of needing intensive care treatment for COVID-19 (OR 0.92, 0.86-0.99), a lower risk of needing respiratory support (OR 0.81, 0.74-0.88) and lower odds of mortality (OR 0.82, 0.75-0.89).[30]

In a systematic review including 12 studies, the authors examined whether influenza vaccination affects the risk of being infected with SARS-CoV-2, and the risk of complicated illness or poor outcomes in COVID-19 patients, being all of them confirmed by PCR. They concluded that influenza vaccination is unlikely to be associated with an increase in the risk of COVID-19 infection or severity and the risk of associated death.[31]

There are reports from some countries with high influenza vaccination rates and high incidences of COVID-19 cases and mortality.[32,33] For instance, Kline et al. compared people vaccinated against flu with non-vaccinated admitted to hospital for COVID-19 and found no differences in admission to intensive care unit (ICU), intubation or other complications.[33] Our results follow these same trends in a general population cohort attended in PHC, not only hospitalized patients.

Limitations

We need to take into account that the present results correspond to the first wave of the pandemic, when there were more negative outcomes and mortality due to COVID-19 than in the subsequent waves occurred in our setting, thus, this higher statistical power allowed us to detect differences. Also, in the next waves more confounders might be involved, such as COVID-19 vaccination or effects of the different variants of the virus, making more difficult to manage their potential effect in the analysis of the outcomes of the infection.

We also need to bear in mind that the target population for the flu vaccine in our country are people older than 60, patients with chronic comorbidities or immunodeficiency, and health care workers, among others,[34] some of them being at high risk of suffering COVID-19 complications, and that is why those confounding variables were used for the adjustment in the logistic regression model.[35] Nevertheless, estimates of influenza vaccine effectiveness have been frequently confounded, pointing out that a different approach should be used with alternative study designs, different from the typical methods used to study drug exposure.[36–38]

Among other limitations of our study there is the reliability of the COVID-19 diagnoses; we included patients without a confirmed result as during the first wave of the pandemic in our setting PCR test were not always performed. This limitation has been described in other research as during the beginning of the pandemic diagnosis test for COVID-19 were not widely available, and clinical algorithms have been used to assess COVID-19 diagnosis.[39] As stated in the Methods section, we compared our number of COVID-19 cases with the official COVID-19 cases provided by the AQuAS during the pandemic.[24] Another limitation is the lack of hospital information: we cannot capture ICU admission, ventilation or treatments administered during the admission, which clearly have influence in the prognosis and outcomes of COVID-19. Finally, we have not conducted any subgroup analysis that might have pointed out any condition which could result in any benefit or harm from the flu vaccination. Conclusions

In conclusion, we were not able to find a protective role of the immunity conferred by the influenza vaccine on the outcomes of the COVID-19 infection. Despite that, our study adds more evidence to the analysis of the possible link between the quality of the immunity and the COVID-19 outcomes, and it has some strengths, such as the large number of patients included, the representativeness with respect to the general population, and the complete socio-demographic data. We have already highlighted that our cohort are PHC patients, so we have estimated the risk of complications for a different population from the hospitalized ones that are usually analyzed in multiple studies.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

ACE2: Angiotensin-converting enzyme-2
AEMPS: Agencia Española de Medicamentos y Productos Sanitarios
AQuAS   : Catalany Agency of Health Quality and Evaluation
ATC: Anatomical therapeutic chemical classification system
BMI: Body mass index
COVID-19: Coronavirus disease 2019
ECAP: Electronic health records in the Catalan Health Institute
ICD-10: International classification of diseases, version 10
ICU: Intensive care unit
LTCF: Long-term care facilities
MEDEA: Socioeconomic index
OR: Odds ratio
PCR: Polymerase chain reaction
PHC: Primary health care
RNA: Ribonucleic acid
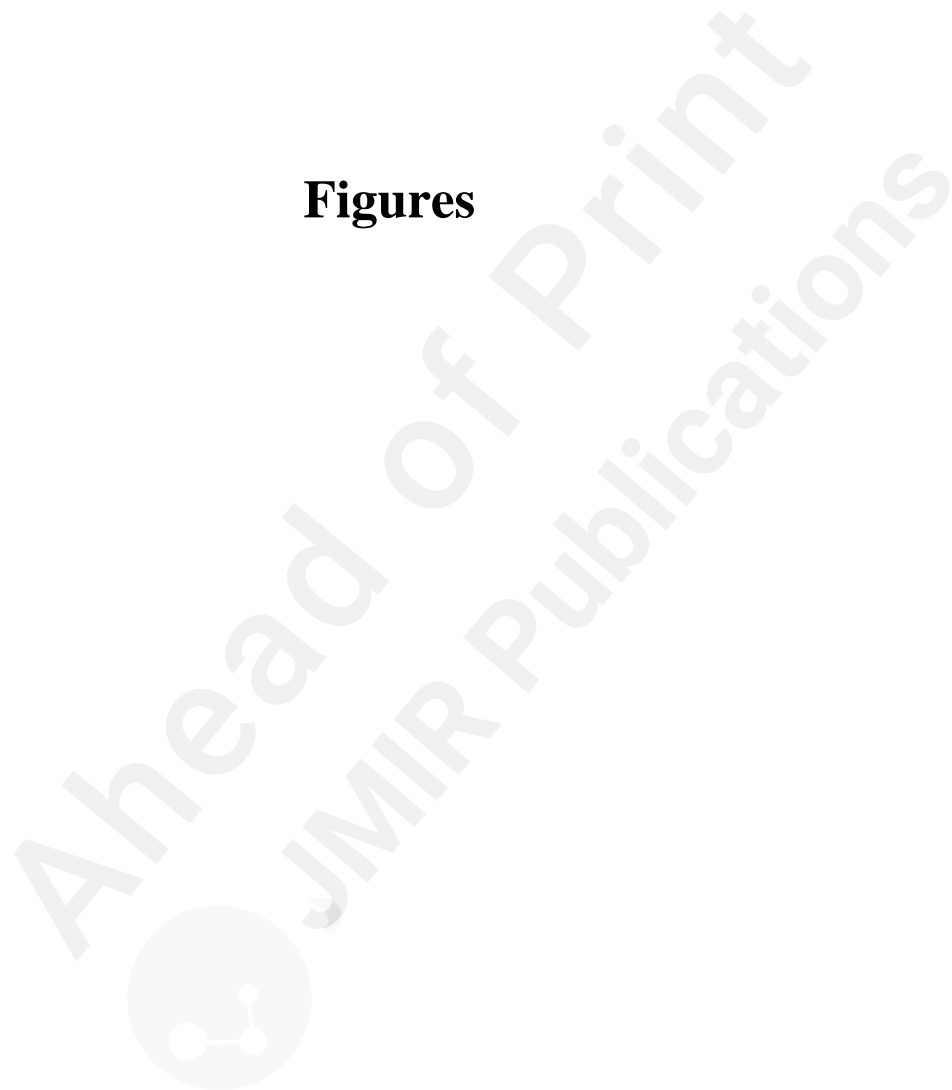SARS-CoV-2: Severe acute respiratory syndrome-2
SIDIAP: Information system for research in primary care
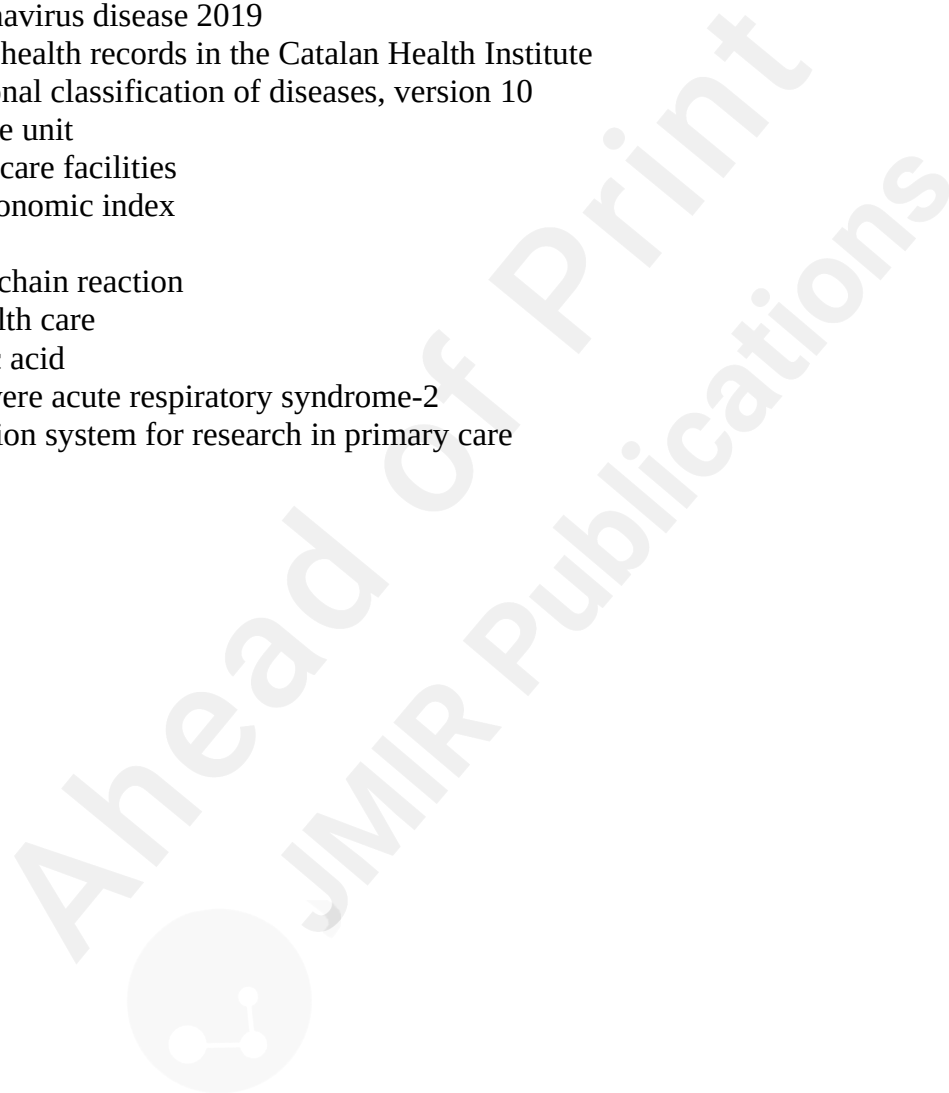
Supplementary Files
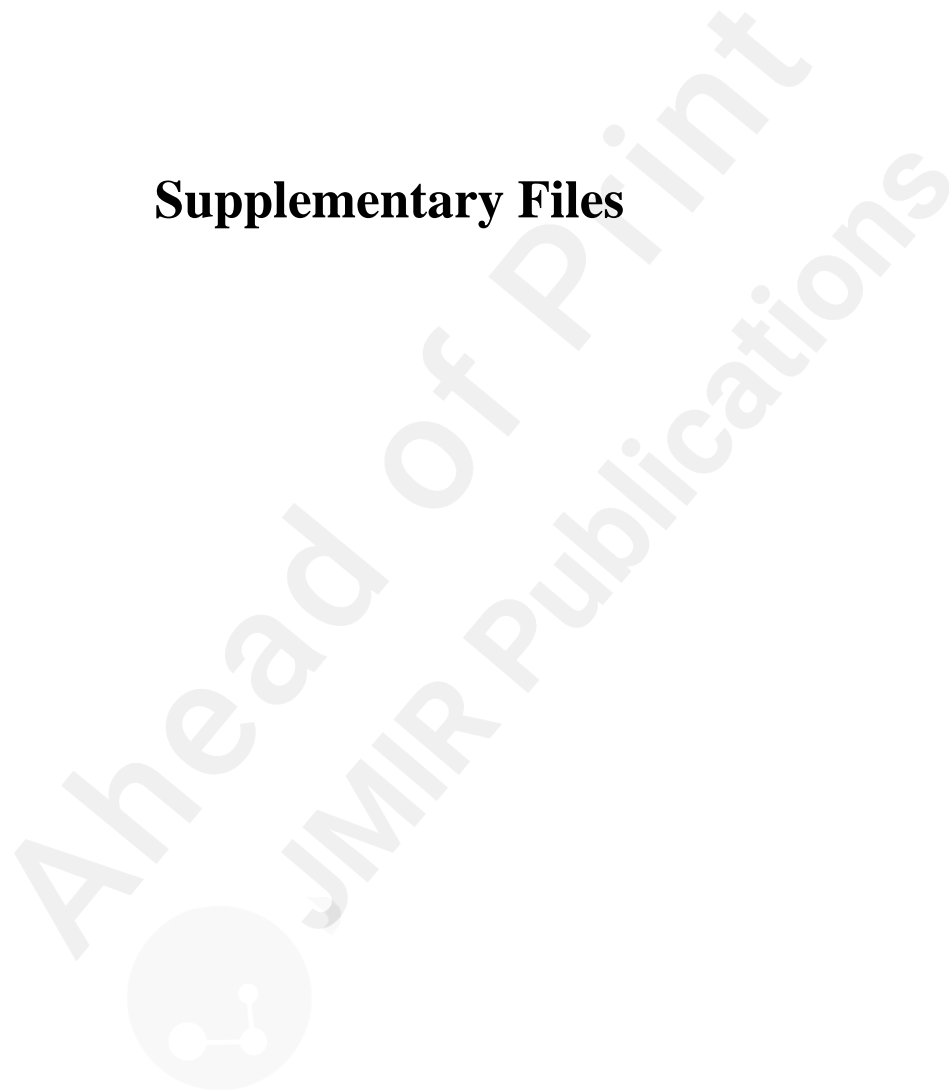
Figures

COVID-19 cases between March and July 2020 according to Catalan Agency of Health (source: https://dadescovid.cat/?lang=eng) compared to SIDIAP database.

Figure S1. COVID-19 cases between March and July 2020 according to Catalan Agency of Health (source: https://dadescovid.cat/?lang=eng) compared to SIDIAP database
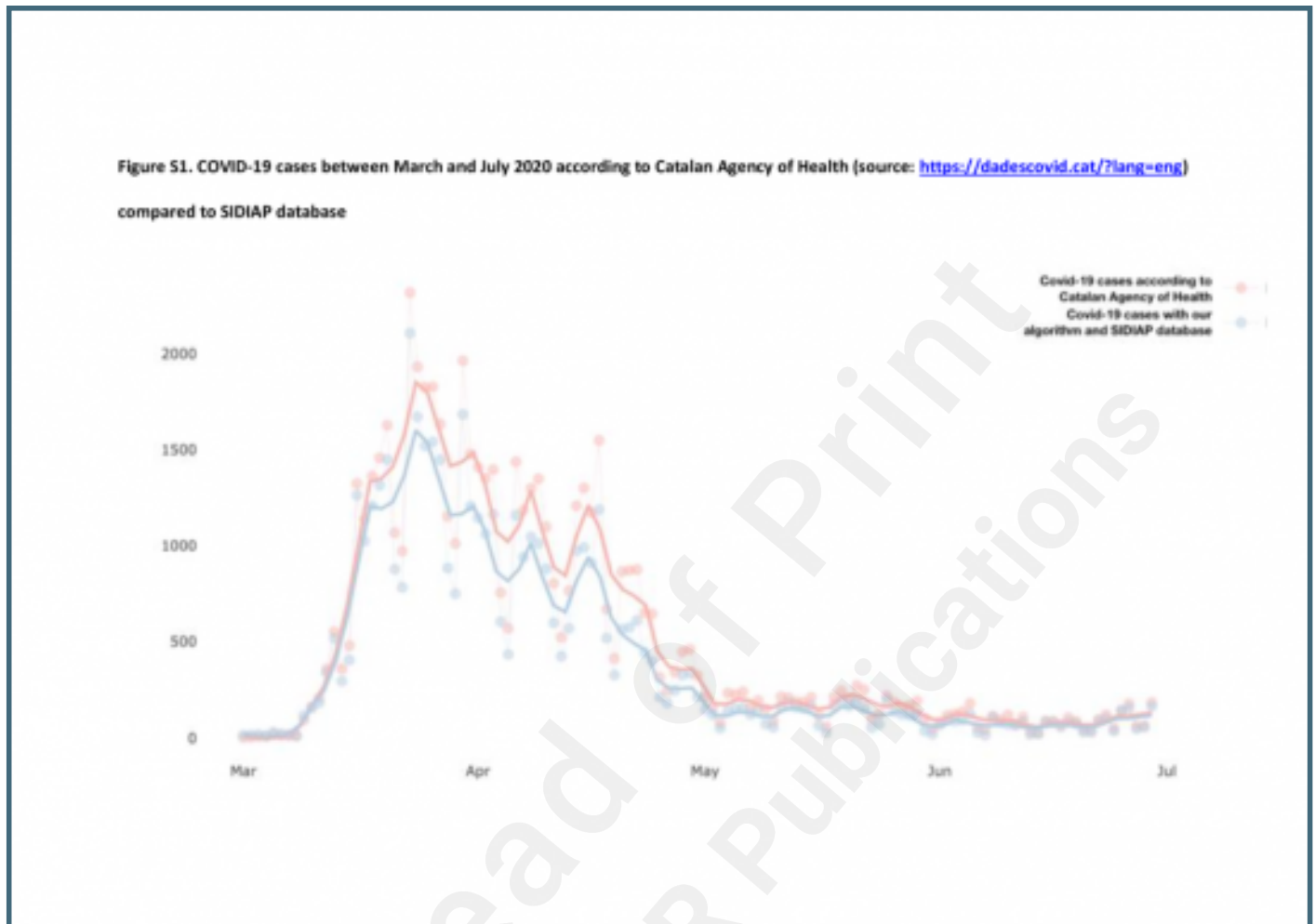
Risk of death and of combined COVID-19 complications in all the vaccinated population and excluding people living in long-term care facilities. LTFC: long-term care facilities. OR: odds ratio. IC 95%: 95% confidence interval. Combined negative outcome includes hospital admission, pneumonia and death. The first forest plot describes the mortality odds in those vaccinated any time before COVID-19 and in those vaccinated excluding LTFC residents. The second forest plot describes the odds for the combination of outcomes in the vaccinated any time before COVID-19 and in the vaccinated excluding LTFC residents.
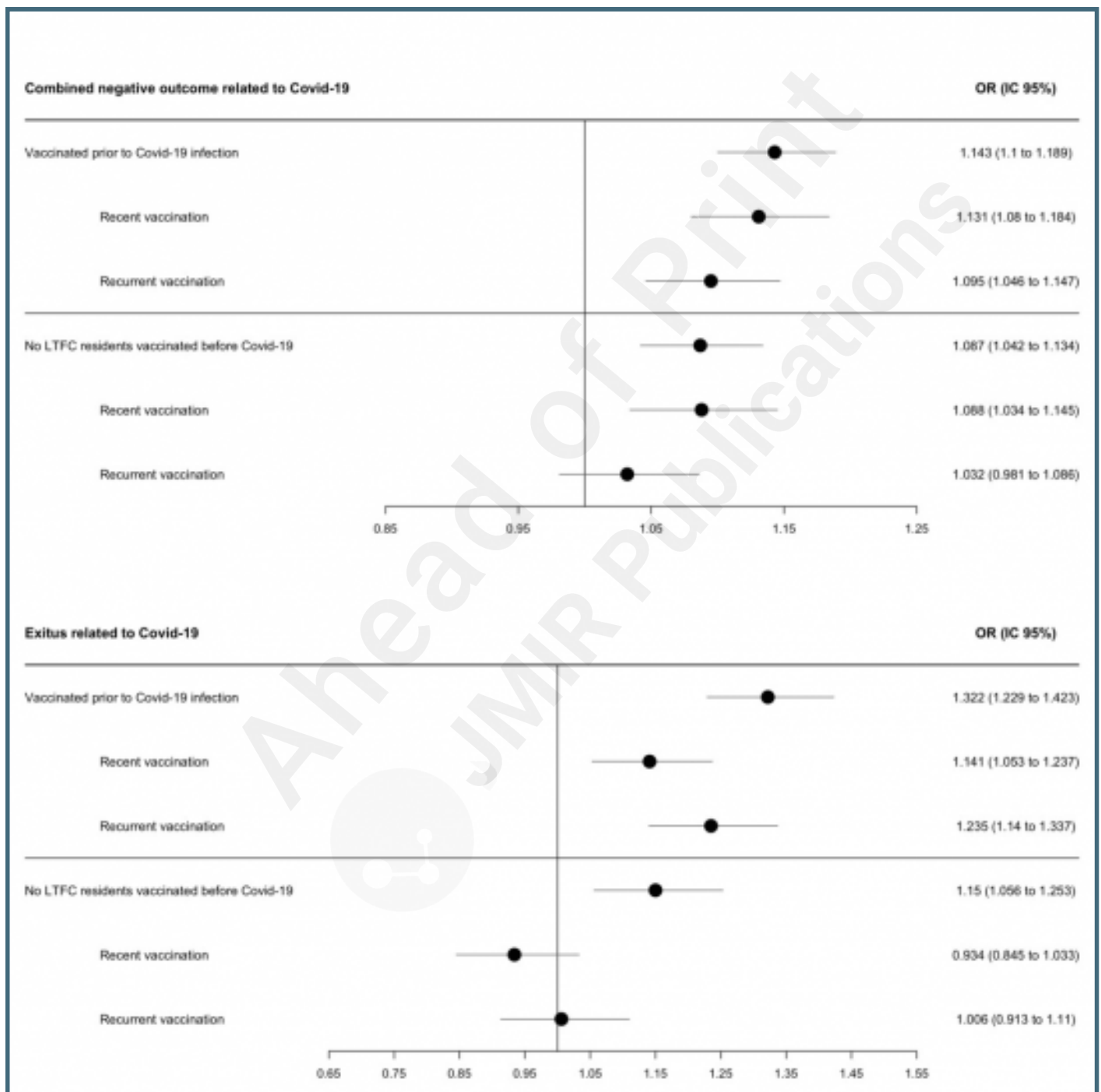
Multimedia Appendixes
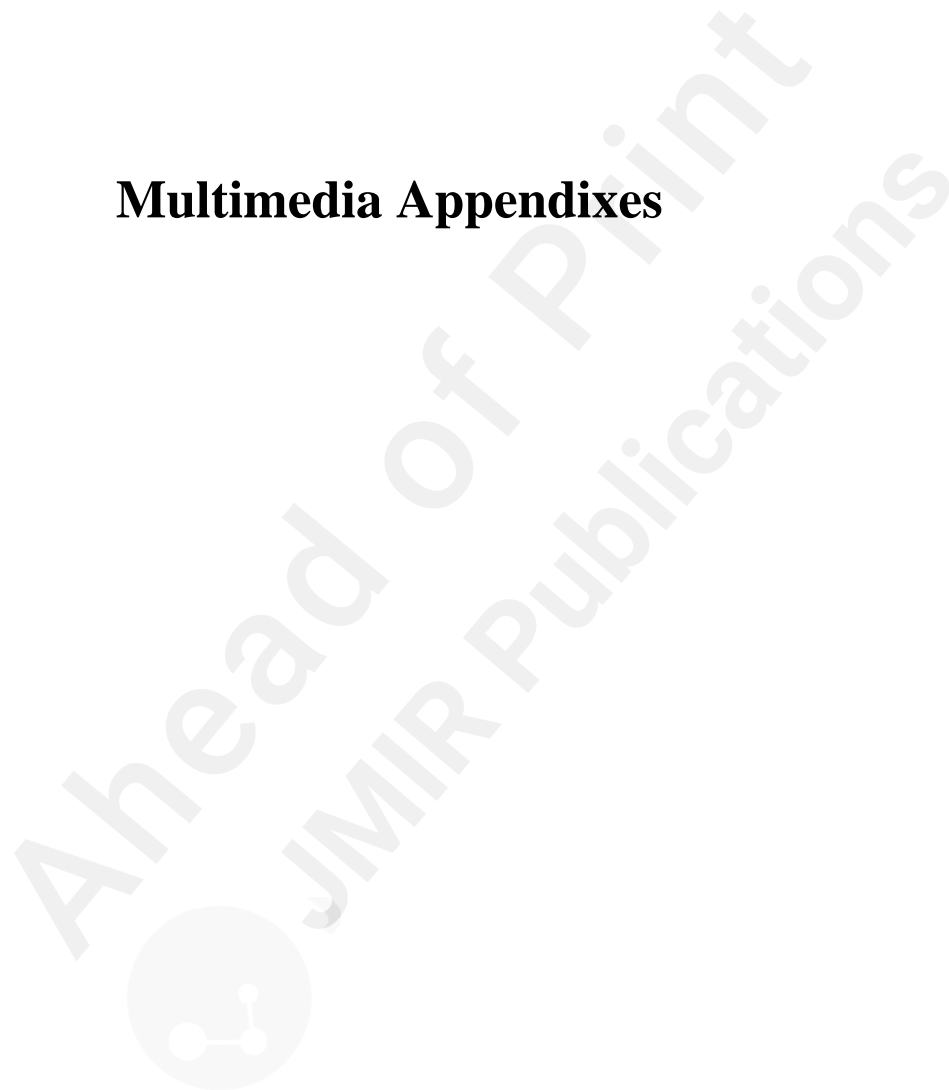
Supplementary table 1. Baseline characteristics of the population included by gender.
URL: http://asset.jmir.pub/assets/d10db7cd3599168729676a5d289b7833.docx

Supplementary table 2. Conditional logistic regression model for the age and gender matched population. Matching performed in patients ? 65 years old to correct for age distribution.
URL: http://asset.jmir.pub/assets/28e5180cb3268dea58ddb3eeafa8e11a.docx

Supplementary table 3. OR.
URL: http://asset.jmir.pub/assets/a2598e43e6f40b12b450c3c52d30808f.xlsx

Manuscript with tracked changes.
URL: http://asset.jmir.pub/assets/ab20fa10b6627addad850df12d986914.docx