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RESEARCH LETTER

Influenza vaccination and prognosis for COVID-19 in hospitalized patients with diabetes: Results from the CORONADO study

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1 | INTRODUCTION

Co-morbidities like diabetes confer higher susceptibility to several respiratory diseases such as influenza, invasive pneumococcal disease, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and a greater risk of death in infected patients.[1,2] For this reason, various organizations recommend routine vaccination against influenza and invasive pneumococcal disease to reduce the risk of hospitalization and death.[3] During the current coronavirus disease 2019 (COVID-19) pandemic, which has resulted in more than 205 million cases and more than 4.3 million deaths worldwide as of 12 August 2021,[4] it has been suggested that influenza vaccination might attenuate its severity.[5-7] Recent reports suggest that prior influenza vaccination is associated with decreased positive COVID-19 testing, is potentially protective from moderate and severe cases of COVID-19 with a lower incidence of clinical outcomes such as hospitalization or mortality regardless of co-morbidities, and reduces the burden of COVID-19.[6,7] Conversely, an analysis of literature review found no evidence of a potentially protective role of the influenza vaccination in COVID-19 patients with influenza co-infection in terms of morbidity and mortality reduction.[8] Two theories have been provided to explain the association between lower odds of hospitalization or death in COVID-19–positive patients and prior administration of influenza vaccine.[9-11] The first one is related to the MF59 adjuvant within the flu vaccine, which may induce protective effects against COVID-19 by triggering a heightened immune response.[11] The second theory concerns the enhancing role of the flu vaccine in the activation of NK cells, which counterbalances the dramatically lower NK cell activity induced by SARS-CoV-2 infection.[9,10] Given the discrepant conclusions from the literature and the low prevalence of patients with diabetes (10%-13%) in these studies,[6,7] more data are needed regarding the possible association between influenza vaccination and COVID-19 severity among patients with diabetes. The coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, designed to describe the phenotype characteristic and prognosis for patients with diabetes admitted with COVID-19 infection in 68 French

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hospitals during the first wave of the pandemic, provided an opportunity to address this matter.[12] In the current analysis, we therefore report data on an association between influenza vaccination during the year before hospitalization and COVID-19–related severe outcomes in patients with diabetes.

2 | METHODS

Data used for the current analysis were obtained from the nationwide multicentre observational CORONADO study (ClinicalTrial.gov NCT04324736). The protocol and study design have been previously reported elsewhere.[12] The influenza vaccination status was obtained from each patient/family by asking if they had been vaccinated against influenza in the current season. Only patients with available information on vaccination status were considered in the analysis. The composite primary outcome (CPO) combined invasive mechanical ventilation and/or death within 7 days.[12] Secondary outcomes were invasive mechanical ventilation, death, and admission to an intensive care unit (ICU) within 7 days and similar outcomes (including CPO) 28 days after hospitalization.

Descriptive statistics (frequencies and percentages, mean and standard deviations [SD], or median and interquartile ranges) were used to present the demographic and clinical characteristics of participants at baseline. For comparisons between vaccinated and unvaccinated patients, appropriate tests were used (*t* test or Wilcoxon for quantitative variables and Fisher's exact test for categorical variables). Cox and logistic (for ICU admission) regression models were used to compare the difference in COVID-19–related severity between vaccinated and unvaccinated patients. To account for missing data, we performed multiple imputation by chained equations with five replications. Then we computed a propensity score (PS) to control for confounding factors that might influence vaccination uptake. Thus, the analyses with and without adjustment were performed on the same number of patients. Adjusted Cox and logistic regressions were applied to estimate the average effect on influenza vaccine as inverse probability of treatment weighting (IPTW).[13] The standardized mean difference method was used to assess the balance of covariates between the vaccination groups before and after weighting. Assumption of hazard proportionality and log-linearity were verified. All data analyses were conducted with R software (4.0.3).

3 | RESULTS

Of the 2798 patients included in the CORONADO study, information on influenza vaccination status was available for 819 (29.3%). Clinical and biological characteristics prior to and upon admission were balanced between patients with and without available information on influenza vaccination (data not shown). A total of 762 (93%) patients tested positive for SARS-CoV-2, and 375 (45.8%) reported having been vaccinated against influenza during the current season. Compared with non-vaccinated patients, those who received the influenza vaccine were older (mean age 73.8 [SD 12.4] vs. 64.4 [13.5] years; $P < .001$), had a longer history of diabetes (14.9 [11.1] vs. 9.8 [8.9] years; $P < .001$), more complications including chronic kidney disease (40.4% vs. 23.3%; $P < .001$), heart failure (15.7% vs. 8.4%; $P = .002$), microangiopathy (51.7% vs. 31.5%; $P < .001$), and macroangiopathy (46.4% vs. 29.6%; $P < .001$), and were more often affected by comorbidities such as hypertension (81.7% vs. 69.7%; $P < .001$), dyslipidaemia (53.5% vs. 42.1%; $P = .002$), and treated obstructive sleep apnoea (14% vs. 6.7%; $P = .001$). Upon admission, vaccinated

TABLE 1 Association between the previous influenza vaccine intake versus no vaccine intake and COVID-19 clinical outcomes estimated in the Cox model (combined primary outcome, invasive mechanical ventilation, and death) and in the logistic regression model (ICU admission) weighted by participants' inverse probability of vaccine

	D7				D28			
	Unadjusted model		Adjusted model[a]		Unadjusted model		Adjusted model[a]	
	HR (95%, CI)	*P* value	HR (95%, CI)	*P* value	HR (95%, CI)	*P* value	HR (95%, CI)	*P* value
Primary outcome	1.25 (0.96-1.63)	.0914	0.90 (0.56-1.45)	.6756	1.25 (0.96-1.63)	.0914	1.04 (0.68-1.57)	.8470
Invasive mechanical ventilation	0.58 (0.39-0.85)	**.0049**	0.67 (0.35-1.25)	.2069	0.61 (0.42-0.88)	**.0088**	0.69 (0.37-1.28)	.2362
Death	3.52 (2.02-6.11)	**<.001**	1.27 (0.52-3.13)	.5947	2.31 (1.61-3.33)	**<.001**	1.35 (0.76-2.39)	.3093
Reanimation admission[b]	0.93 (0.88-0.98)	**.0155**	0.94 (0.86-1.03)	.1729	0.93 (0.87-0.98)	**.0152**	0.94 (0.86-1.03)	.1763

Note: Bolded p values were < 0.05, which means the influenza vaccine was significantly associated with outcomes (combined primary outcome, invasive mechanical ventilation, and death).

[a]The propensity score was constructed for age, sex, body mass index, tobacco use, alcohol use, history of hypertension, ischaemic heart disease, heart failure, stroke, peripheral artery disease, diabetic kidney disease, retinopathy, dyslipidaemia, HbA1c, respiratory failure and/or chronic obstructive pulmonary disease, treatment for obstructive sleep apnoea, active cancer, and the use of metformin, insulin, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1, statin, thiazide diuretic, potassium-sparing diuretic, acarbose, sulphonylurea/glinide, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, beta blocker, antiplatelet agent, and anticoagulant.

[b]For ICU admission, the vaccine effects size was expressed using odds ratio.

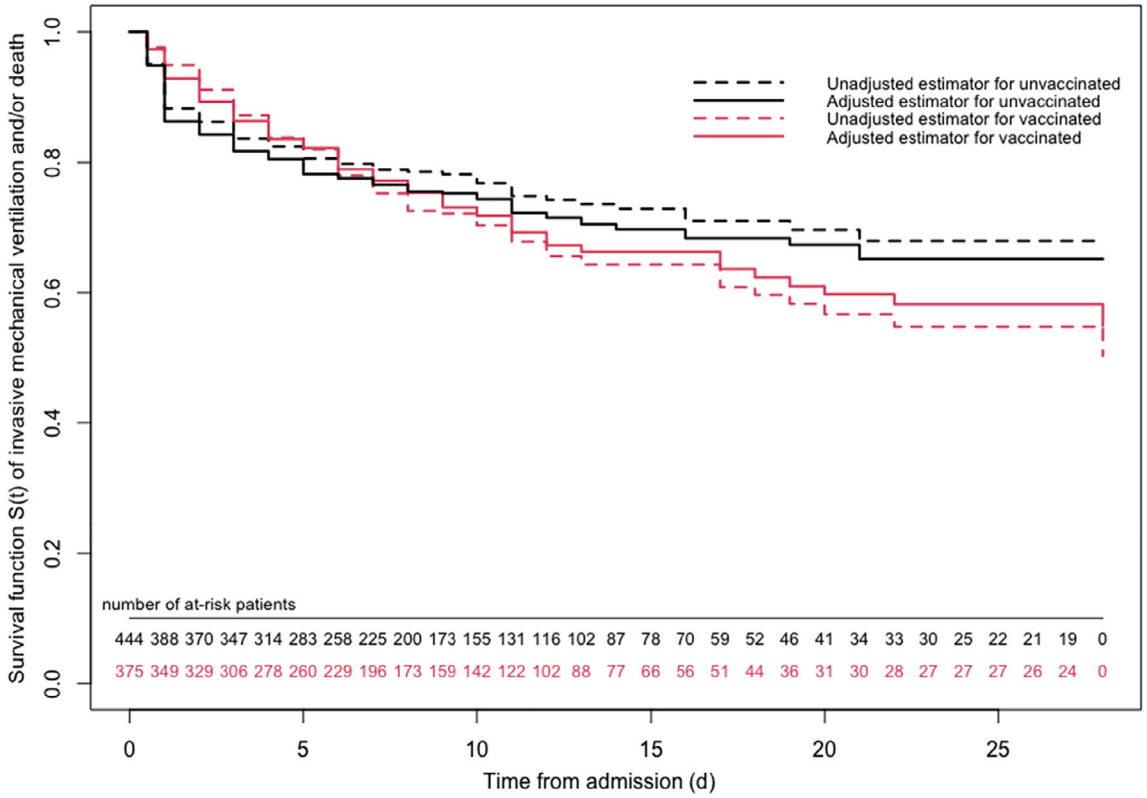

FIGURE 1 Kaplan–Meier curve for invasive mechanical ventilation and/or death in the unweighted sample (dotted lines) and the sample used for inverse probability of treatment weighting (dashed lines). The propensity score was constructed for age, sex, body mass index, tobacco use, alcohol use, history of hypertension, ischaemic heart disease, heart failure, stroke, peripheral artery disease, diabetic kidney disease, retinopathy, dyslipidaemia, HbA1c, respiratory failure and/or chronic obstructive pulmonary disease, treatment for obstructive sleep apnoea, active cancer, and the use of metformin, insulin, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1, statin, thiazide diuretic, potassium-sparing diuretic, acarbose, sulphonylurea/glinide, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, beta blocker, antiplatelet agent, and anticoagulant

patients had a shorter time between the onset of COVID-19 symptoms and hospital admission (median 5.0 [IQR 2.0 to 8.5] vs. 6.0 [3.0 to 10.0]; $P = .002$), better glycaemic control (HbA1c: median 7.5% vs. 8.0%; $P < .001$), and lower estimated glomerular filtration rate (measured using the Chronic Kidney Disease Epidemiology Collaboration equation; 64.6 vs. 80.1 mL/min/1.73m^2; $P < .001$), haemoglobin (12.7 vs. 13.1 g/L; $P = .013$), lymphocyte count (950 vs. 1100 10^3/mm^3; $P < .001$), and platelet count (201 vs. 208 10^3/mm^3; $P = .046$). COVID-19 symptoms (94.4% vs. 95.3%; $P = .687$), liver biomarkers (gamma-glutamyl transferase: 0.90% vs. 1.0% upper limit of normal; $P = .998$), and C-reactive protein (70.4 vs. 80.9 mg/L; $P = .097$) did not differ between vaccinated and unvaccinated patients. Complete data on the clinical and biological characteristics of the two vaccine groups are provided in Table S1. In the non-weighted analyses, among the 444 patients who were not vaccinated, the rate of invasive mechanical ventilation and/or death within 28 days was 24% compared with 31% in the vaccinated group (hazard ratio 1.25, 95% confidence interval 0.96-1.63; Table 1 and Figure 1). The overall survival rate at 28 days was 23% in the vaccinated group and 10% in the unvaccinated group (2.31, 1.61-3.33). The corresponding invasive mechanical ventilation and ICU admission rates were 11% versus 24% (0.61, 0.42-0.88) and 23% versus 30% (0.93, 0.87-0.98), respectively. In the IPTW-adjusted analysis (Figure S1), no significant association was found between influenza vaccination and the primary outcome (1.04, 0.68-1.57) or its individual component at day 7 or day 28 (Table 1).

4 | DISCUSSION

To the best of our knowledge, this is the first study to address the impact of seasonal influenza vaccination on COVID-19 severity in patients with diabetes.

While we did not find an association between influenza vaccination and the severity of COVID-19, two recent US studies have shown a beneficial effect of influenza vaccination.[6,7] The first study concerns a research databank consisting of 2005 patients tested for COVID-19 in the University of Florida Health system, and indicates that, compared with 214 (10.7%) COVID-19–positive patients who received the influenza vaccine during the previous year, those who had not been vaccinated had 2.44 (95% CI 1.68-3.61) greater odds of hospitalization, and 3.29 (1.18-13.77) greater odds of ICU admission.[7] The second large study involved 27 210 patients tested for COVID-

19 within the Michigan healthcare system, of whom 12 997 (48%) received a flu vaccine. The study's objectives were to explore the relationship between influenza vaccination and COVID-19, and for those patients with COVID-19, to compare the severity of COVID-19 and mortality risk according to influenza vaccination status. The authors concluded that the influenza vaccine reduced the odds of testing positive for COVID-19 by 24% (risk ratio 0.76, 95% CI 0.68-0.86). Moreover, in COVID-19–positive patients, the influenza vaccine reduced the odds of hospitalization, invasive mechanical ventilation, and length of hospital stay by 42% (0.58, 0.46-0.73), 55% (0.45, 0.27-0.78), and 24% (0.76, 0.65-0.89), respectively.[6]

One possible explanation for this observed discrepancy compared with our report is that CORONADO patients were older and more frequently affected by co-morbidities, and therefore were associated with a more severe clinical and biological presentation upon admission. Indeed, in the two US studies, the mean age of patients ranged from 40.7 to 48.4 years with a prevalence of diabetes of 9%-11%,[6,7] whereas all our patients had diabetes. Another possible explanation for this discrepancy is the difference in statistical method used to estimate the influenza vaccine effect, especially in the Florida report, with an absence of the inverse probability of treatment weighting by covariates to control for confounders.[7]

In the current study, information on influenza vaccination was available for 29.3% of the whole sample, of whom 46% received the vaccine, while 28% were followed by a diabetologist. Despite the annual seasonal influenza vaccination (SIV) recommendation for people with diabetes, in most Western countries the SIV rate is below the World Health Organization's target of 75% (e.g. 30% among those aged <65 years and 60% among those aged ≥65 years in France during 2015/2016).[14,15] The complexity of the vaccination pathway in France, vaccine reluctance, change of general practitioners (GPs) or less frequent contact with GPs, absence of co-morbidities or previous hospitalization stay for diabetes or influenza, and the low involvement of diabetologists, have all been suggested as explanations for the low SIV rate in this population.[15]

Although the amount of missing information on vaccination status and the limited size of the study population contributed to limiting the power to detect a significant difference, our study has some strengths. First, it is a multicentre study that recruited patients from 68 French hospitals, making it generalizable to those inpatients with diabetes admitted for COVID-19 in France. Second, we used a rigorous statistical method approach to account for potential confounders, especially PS, to estimate the effect of the influenza vaccine. Finally, clinical and biological characteristics were balanced between patients with and without available information on the influenza vaccination (data not shown), which might contribute to attenuate selection bias.

In conclusion, these results confirm the safety of annual influenza vaccination in patients with diabetes with respect to COVID-19. Our results should encourage authorities to strengthen co-vaccination programmes against seasonal influenza and COVID-19 in this high-risk population to achieve sufficient coverage rates to reduce morbidity and mortality.

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CONFLICT OF INTEREST

AD, FG, AS, and J-BB declare no conflict of interest. BC reports grants and personal fees from Amgen, AstraZeneca, Akcea, Genfit, Gilead, Eli Lilly, Novo Nordisk, and MSD, and grants and personal fees from Sanofi and Regeneron. PG reports personal fees from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Mundipharma, Sanofi, and Servier, and grants and personal fees from Novo Nordisk. SH reports personal fees and non-financial support from AstraZeneca, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, grants from Dinno Santé, personal fees from Eli Lilly, non-financial support from LVL, personal fees and non-financial support from MSD, personal fees from Novartis, grants from Pierre Fabre Santé, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Servier, and personal fees from Valbiotis. MP reports personal fees and non-financial support from Novo Nordisk, and non-financial support from Sanofi and Amgen. MW reports personal fees from Novo Nordisk.

AUTHOR CONTRIBUTIONS

AD analysed data and wrote the first draft. FG and AS initiated the study, interpreted the data, and reviewed the manuscript. MW and J-BB realized data preparation and reviewed the manuscript. BC, PG, MP, and SH designed the CORONADO study and reviewed the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data available on request from the authors The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323(16):1612.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
3. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes—2021. *Diabetes Care*. 2021;44(suppl 1):S40-S52.
4. Johns Hopkins University. Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU); 2020. https://coronavirus.jhu.edu/map.html. Accessed September 10, 2020.
5. Sultana J, Mazzaglia G, Luxi N, et al. Potential effects of vaccinations on the prevention of COVID-19: rationale, clinical evidence, risks, and public health considerations. *Expert Rev Vaccines*. 2020;19(10):919-936.
6. Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the influenza vaccine on COVID-19 infection rates and severity. *Am J Infect Control*. 2021;49(6):694-700.
7. Yang M-J, Rooks BJ, Le T-TT, et al. Influenza vaccination and hospitalizations among COVID-19 infected adults. *J Am Board Fam Med*. 2021;34(suppl):S179-S182.
8. Thindwa D, Garcia Quesada M, Liu Y, et al. Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality. *Vaccine*. 2020;38(34):5398-5401.
9. Jewett A. The potential effect of novel coronavirus SARS-CoV-2 on NK cells; a perspective on potential therapeutic interventions. *Front Immunol*. 2020;11:1692.
10. Jost S, Altfeld M. Control of human viral infections by natural killer cells. *Annu Rev Immunol*. 2013;31(1):163-194.
11. Gupta T, Gupta SK. Potential adjuvants for the development of a SARS-CoV-2 vaccine based on experimental results from similar coronaviruses. *Int Immunopharmacol*. 2020;86:106717.
12. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. 2020;63(8):1500-1515.
13. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med*. 2010;29(20):2137-2148.
14. Verger P, Fressard L, Cortaredona S, et al. Trends in seasonal influenza vaccine coverage of target groups in France, 2006/07 to 2015/16: impact of recommendations and 2009 influenza A(H1N1) pandemic. *Euro Surveill*. 2018;23(48):1700801.
15. Bocquier A, Cortaredona S, Fressard L, Galtier F, Verger P. Seasonal influenza vaccination among people with diabetes: influence of patients' characteristics and healthcare use on behavioral changes. *Hum Vaccin Immunother*. 2020;16(10):2565-2572.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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