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.

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Letter to the Editor

Letter in response to article in journal of infection: Impact of routine infant BCG vaccination on COVID-19

To the Editor,

We read with great interest the study by Kinoshita and Tanaka in which the association of the BCG vaccine coverage with the prevalence of SARS-CoV-2 infection was analysed.[1]

In Italy, BCG vaccine was introduced mandatorily in 1975 for close contacts of Tuberculosis (Tb) cases, healthcare workers (HCWs), medical students and military forces. In 2001 these recommendations were reviewed and BCG became mandatory for children under 5 years of age, close contacts of Tb cases and medical, nursing students and HCWs employed in high-risk settings.[2]

In Tuscany, Central Italy, the COVID-19 epidemic broke out at the end of February 2020, and as of May 28th, 2020, the Region counted over 10,000 COVID-19 confirmed cases.[3]

Thanks to the availability of the information on BCG vaccination status among COVID-19 cases occurred in the territory of Central Tuscany Health Unit, which covers over 1,6 million residents, we conducted a study aimed at assessing the correlation between BCG vaccination and the severity of COVID-19 in patients between 20 and 75 years, considering sex, age, comorbidities and being a healthcare worker (HCW) as confounders in a multivariate logistic regression model.

The data source for SARS-CoV-2 infections was represented by a database developed within the national integrated COVID-19 surveillance system by the Italian National Institute of Health, comprising information on COVID-19 laboratory-confirmed cases, i.e. demographic characteristics; the date of symptoms onset; disease severity and outcome; risk factors such as obesity or being a healthcare worker.

An anonymized database by replacing cases' identifying variables with the universal anonymous identifier (IdUni) adopted within electronic health records of the Regional Health System of Tuscany was created. Through the IdUni, it was possible to assess previous vaccination with BCG, as well as the presence of chronic diseases, using the MaCro dataset of the Regional Health Agency,[4] or active cancer by linking the IdUni with the hospital discharge record dataset to identify patients with at least one hospitalization for malignant cancer in the previous five years.

As patient data were anonymized, approval from the local ethics committee was not required.

COVID-19 outcomes were dichotomized as recovery without the need to access hospital treatment versus hospitalization or death.

Among 2908 SARS-CoV-2 infections diagnosed between 02/24/2020 and 05/28/2020, 63 (2.2%) occurred in vaccinees, 40 of them HCWs.

In Table 1, the demographic and clinical characteristics of SARS-CoV-2 infected individuals and their outcomes according to the BCG vaccination status are showed. Almost two out of three among vaccinees ($N = 40$) were HCWs.

When each covariate was individually considered through logistic regression analyses adjusting only for age and gender (Table 2), consistently with the evidence emerging across the world, [5–7] gender, age, obesity and several chronic conditions were correlated with a bad COVID-19 outcome; furthermore, BCG and HCW status were protective against the risk of severe COVID-19: for BCG vaccine Odds Ratio (OR)= 0.47 (95% CI 0.22–0.98).

Variables with a significance level of $p < 0.10$ in such analyses were entered in a subsequent multivariate logistic regression model, in which they were considered statistically significant when the p-value was less than 0.05; chronic diseases with a significance level of $p < 0.10$ in the first analyses were assessed together as a binary category (having at least one chronic disease/having no comorbidity). Age, gender and obesity were shown to be independent determinants of a poorer outcome, as well as the presence of at least one comorbidity among those for which a significant association with the outcome in the univariate analysis was observed (i.e. ischemic heart disease, myocardial infarction, peripheral obliterative arteriopathy, stroke, hypertension, diabetes mellitus, COPD and dyslipidaemia) ($p<0.001$) (Table 2). On the contrary, being a HCW was inversely and independently correlated with a poorer outcome (OR=0.30, 95% CI 0.23–0.39). BCG was inversely correlated with the risk of being hospitalized or dying from COVID-19, although this association was not significant (OR=0.71, 95% CI 0.33–1.51).

Since a strong interaction between being vaccinated with BCG in the past and being a healthcare worker was observed ($p = 0.007$), the multivariate analysis was repeated to consider separately i) the general population, i.e. all except healthcare workers and ii) healthcare workers only. In the general population, 23 were those vaccinated and 2142 those not vaccinated; BCG was strongly associated with a more favorable outcome (adjusted OR =0.09; 95% CI 0.01–0.74). If the risk among vaccinated individuals were the same as among non-vaccinated, we would have observed an unfavorable outcome in eight cases, whereas only one hospitalization was observed and no deaths occurred in the group of vaccinees.

On the other hand, this supposed protective role of BCG against a poorer outcome was no longer evident among HCWs. For HCWs the adjusted OR was 1.87 (95% CI 0.81–4.33). Mass screening interventions for SARS-CoV-2 infections have been implemented among HCWs in Tuscany since April 2020.[8] Such interventions allowed for asymptomatic infections in this group to emerge, which may at least partially explain the inverse association observed between being a HCW and the risk of developing a severe form of COVID-19. In Tuscany, the first epidemic wave in spring 2020 had less serious consequences than in the northern regions of Italy; the national lockdown imposed on account of the acceleration of the outbreak in the north of the country between February and March came into effect in Tuscany in an earlier epidemic phase, and granted HCWs

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Table 1
Characteristics of SARS-CoV-2 infected individuals according to the BCG vaccination status.

	BCG vaccine				
	N (%)	No ($N = 2845$; 97.8%) N (%)	Yes ($N = 63$; 2.2%) N (%)	Total ($N = 2908$)	p value
Sex	Male	1310 (46.0)	17 (27.0)	1327 (45.6)	**0.003**
	Female	1535 (54.0)	46 (73.0)	1581 (54.4)	
Age	Mean age (SD)	53.3 (13.7)	47,6 (12.0)	53.2	**<0.001**
Body mass index (BMI)[a]	<30	2790 (98.1)	63 (100)	2853 (98.1)	0.265
	>30	55 (1.9)	0 (0.0)	55 (1.9)	
Chronic diseases	None	1504 (52.9)	32 (50.8)	1536	0.745
	Heart failure	56 (2.1)	0 (0.0)	56 (2.1)	0.254
	Ischemic heart disease	118 (4.5)	1 (1.7)	119 (4.4)	0.296
	Myocardial infarction	59 (2.2)	0 (0.0)	59 (2.2)	0.242
	Peripheral obliterating arteriopathy	50 (1.9)	0 (0.0)	50 (1.8)	0.282
	Stroke	58 (2.2)	0 (0.0)	58 (2.1)	0.246
	Hypertension	916 (34.7)	20 (33.3)	936 (34.6)	0.828
	Diabetes	244 (9.2)	5 (8.3)	249 (9.2)	0.811
	Chronic obstructive pulmonary disease (COPD)	53 (2.0)	0 (0.0)	53 (2.0)	0.268
	Parkinson's disease	30 (1.1)	0 (0.0)	30 (1.1)	0.406
	Chronic kidney disease	4 (0.1)	0 (0.0)	4 (0.1)	0.763
	Multiple sclerosis	8 (0.30)	1 (1.7)	9 (0.3)	0.070
	Dementia	65 (2.5)	2 (3.3)	67 (2.5)	0.668
	Dyslipidaemia	901 (34.1)	18 (30.0)	919 (34.0)	0.506
	Epilepsy	66 (2.5)	2 (3.3)	68 (2.5)	0.683
	Inflammatory bowel disease	21 (0.8)	0 (0.0)	21 (0.8)	0.488
	Chronic rheumatic disease	59 (2.2)	1 (0.7)	60 (2.2)	0.768
Neoplasia	No active tumor	2841 (99.9)	63 (100)	2904 (99.9)	0.766
	Active tumor	4 (0.1)	0 (0.0)	4 (0.1)	
Profession	Not a HCW	2142 (75.3)	23 (36.5)	2165 (74.5)	
	HCW	703 (24.7)	40 (63.5)	743 (25.5)	**<0.001**
Setting	Home dwelling	2772 (97.4)	63 (100)	2835 (97.5)	0.198
	Nursing /residential care facility	73 (2.6)	0 (0.0)	73 (2.5)	
Outcome	At-home recovery	1866 (65.6)	54 (85.7)	1920 (66.0)	**0.001**
	Hospitalization or death	979 (34.4)	9 (14.3)	988 (34.0)	

[a] The info regarding BMI>30 was present for 1574 patients; the 1334 for whom the BMI was not indicated, were considered as having a BMI<30.

Table 2
Logistic regression analyses to assess the association of covariates with the outcome (hospitalization or death). A) Results of logistic regression analyses adjusting only for age and gender; B) Results of the multivariate logistic regression model.

A) Logistic regression analyses to assess the association of each covariate with the outcome adjusting only for age and gender			
	Covariates	OR (95% Conf. Int.)	p-value
Gender[a]	Males VS. females	**2.25 (1.90–2.65)**	<0.001
Age[b]	Age	**1.06 (1.05–1.06)**	<0.001
BMI	>30	**6.07 (3.06–12.07)**	<0.001
Vaccination	BCG vaccine	**0.47 (0.23–0.98)**	0.045
Chronic diseases	Heart failure	1.05 (0.60–1.83)	0.871
	Ischemic heart disease	**1.54 (1.03–2.31)**	0.036
	Myocardial infarction	**1.80 (1.01–3.21)**	0.045
	Peripheral obliterative arteriopathy	**1.97 (1.06–3.65)**	0.031
	Stroke	**1.87 (1.06–3.30)**	0.029
	Hypertension	**1.61 (1.33–1.95)**	<0.001
	Diabetes	**1.70 (1.28–2.26)**	<0.001
	COPD	**2.74 (1.47–5.10)**	0.002
	Parkinson's disease	0.51 (0.22–1.17)	0.113
	Chronic kidney disease	2.70 (0.27–26.6)	0.395
	Multiple sclerosis	0.30 (0.037–2.53)	0.271
	Dementia	0.68 (0.40–1.15)	0.149
	Dyslipidaemia	**1.53 (1.27–1.83)**	<0.001
	Epilepsy	1.22 (0.73–2.05)	0.455
	Inflammatory bowel disease	0.42 (0.15–1.19)	0.103
	Chronic rheumatic disease	1.45 (0.84–2.52)	0.181
Neoplasia	Active tumor	2.74 (0.26–29.04)	0.402
Profession	HCW	**0.29 (0.23–0.37)**	<0.001
Setting	Living in a nursing /residential care facility	0.77 (0.47–1.25)	0.289
B) Results of the multivariate logistic regression analysis			
	Covariates	Adjusted OR (95% Conf. Int.)	p-value
Vaccination	BCG vaccine	0.71 (0.33–1.51)	0.369
Gender	Male VS female	**1.99 (1.68–2.37)**	<0.001
Age	Age	**1.04 (1.03–1.05)**	<0.001
BMI	BMI>30	**5.50 (2.72–11.11)**	<0.001
Chronic diseases[c]	Having at least 1 chronic disease	**1.56 (1.29–1.87)**	<0.001
Profession	Being a HCW	**0.30 (0.23–0.39)**	<0.001

[a] Adjusted for age.
[b] Adjusted for gender.
[c] Among ischemic heart disease, myocardial infarction, peripheral obliterative arteriopathy, stroke, hypertension, diabetes mellitus, COPD and dyslipidaemia.

time for preparation, training, and the adoption of protection measures. Hence, BCG probably could not confer any additional protection on top of that already provided by these prevention and control measures.

Although definitive conclusions can only be drawn from the results of the ongoing RCTs, our findings provided suggestive evidence that BCG vaccination might provide protection against severe forms of COVID-19, and are in line with Kinoshita and Tanaka's observations. Nonetheless, we highlight the need to consider the HCW status as an effect modifier of the association between BCG vaccination and COVID-19 outcomes in observational studies that may be carried out in the near future on larger cohorts to confirm such findings.

Declaration of Competing Interests

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References

1. Masako Kinoshita, Masami Tanaka. Impact of routine infant BCG vaccination on COVID-19. *J Infect* 2020;**81**(4):625–33. doi:10.1016/j.jinf.2020.08.013.
2. *Decree of the President of the Republic. November 7, 2001, n.465, 2001*. n.d.
3. Regional Health Agency of Tuscany. Data on COVID-19 in Tuscany and Italy. Available at https://www.ars.toscana.it/banche-dati/dati-sintesi-sintcovid-aggiornamenti-e-novita-sul-numero-dei-casi-deceduti-tamponi-per-provincia-e-per-asl-della-regione-toscana-e-confronto-con-italia-con-quanti-sono-i-decessi-per-comune?provenienza=home_ricerca&de. Accessed October 28, 2020, 2020.
4. Irene Bellini, Valentina Barletta, Francesco Profili, Alessandro Bussotti, Irene Severi, Maddalena Isoldi, et al. Identifying high-cost, high-risk patients using administrative databases in Tuscany. *Biomed Res Int* 2017;**2017**:1–12. doi:10.1155/2017/9569348.
5. Wei-jie Guan, Wen-hua Liang, Yi Zhao, Heng-rui Liang, Zi-sheng Chen, Yi-min Li, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;**55**(5):2000547. doi:10.1183/13993003.00547-2020.
6. Killerby Marie E, Ruth Link-Gelles, Haight Sarah C, Schrodt Caroline A, Lucinda England, Gomes Danica J. et al. Characteristics associated with hospitalization among patients with COVID-19 — Metropolitan Atlanta, Georgia, March–April 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**(25):790–4. doi:10.15585/mmwr.mm6925e1.
7. Jennifer Lighter, Michael Phillips, Sarah Hochman, Stephanie Sterling, Diane Johnson, Fritz Francois, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa415.
8. Agenzia Regionale di Sanità della Toscana. *Screening for SARS-CoV-2 infection: first results on the validation of rapid tests in the field and on screening of health care workers [Screening per infezione da SARS-CoV-2: primi risultati sulla validazione dei test rapidi sul campo e sullo screening degli operatori sanitari]*. Italy: Florence; 2020.

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