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Short communication

COVID-19 vaccines provide better protection against related pneumonia than previous symptomatic infection

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ABSTRACT

Objectives: To compare, in a real-world scenario, the protective effect of vaccination and previous laboratory-confirmed symptomatic infection on the risk of COVID-19 pneumonia.
Methods: A retrospective study was conducted and 46,998 adults with laboratory-confirmed COVID-19 were enrolled. Risk ratios (RRs) and 95% confidence intervals (CIs) were used to evaluate the effect of the evaluated exposures on the risk of pneumonia.
Results: In multiple analysis and after adjusting by reinfection status, vaccinated participants were at reduced risk of developing pneumonia (RR = 0.974, 95% CI 0.965–0.983). The association of having had a previous infection was not significant (RR = 1.001, 95% CI 0.969–1.034).
Conclusion: Our results suggest, and if later replicated, that COVID-19 vaccines provide better protection against pneumonia than previous symptomatic infections. Therefore, offering vaccination to all eligible subjects despite past COVID-19 infections might be relevant to reducing the pandemic-related burden.

Background

The burden of the COVID-19 pandemic in Mexico has been high and by mid-October 2021, more than 3.7 million laboratory-confirmed cases have been registered, with more than 280 thousand deaths.

The COVID-19 vaccines represent a major step toward ending the pandemic. Published in *vitro data* suggest a better neutralization of some circulating SARS-CoV-2 variants after COVID-19 vaccination when compared with natural infection (Deng et al., 2021; Stamatatos et al., 2021). However, and to the best of our knowledge, studies analyzing the benefit of vaccination for previously infected subjects in a real-world scenario are scarce (Shrestha et al., 2022).

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The aim of this study was to compare the protective effect of vaccination and previous laboratory-confirmed symptomatic infection on the risk of COVID-19 pneumonia. In addition, we evaluated the interaction between both exposures on the risk of severe illness.

Methods

We conducted a retrospective and nationwide cohort study in Mexico. Eligible subjects were adults with laboratory-confirmed COVID-19 (RT-PCR or rapid antigen testing) and symptoms onset from February to July 2021. Participants were identified from nominal records found in a national normative system for the epidemiological surveillance of respiratory viruses.

The vaccinated subjects were those with two doses of any COVID-19 vaccine or a single dose (any COVID-19 vaccine) at 15 or more days before illness onset. The second-time laboratory-confirmed SARS-CoV-2 infection was defined by the reappearance of symptoms of COVID-19 at more than 90 days after the initial laboratory-confirmed illness.

Pneumonia was the main outcome and it was defined by clinical (fever or chills, cough, shortness of breath, and tachypnea) and radiographic findings (ground-glass patterns in x-ray or computed tomography imaging) that required hospital admission. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using generalized linear regression models and were used to evaluate the association between the analyzed exposures and the risk of COVID-19 pneumonia. The interaction between vaccination and reinfection was also tested.

Results

Data from 46,998 participants were analyzed for a total follow-up of 379,475 person-days. The study profile is shown in Supplementary Data 1. The overall frequency of vaccination and second-time infection in the study sample was 3.3% and 0.2%, respectively. Later, the mean (± standard deviation) elapsed days between episodes were 183.9 (± 69.8 days).

The overall rate of pneumonia was 4.4 cases per 1000 person-days, respectively. According to vaccination status, the pneumonia rate was 4.4 and 3.6 cases per 1000 person-days in unvaccinated and vaccinated participants, respectively.

Compared with participants with no severe manifestations, patients with pneumonia were older (mean age ± standard deviation: 61.9 ± 15.0 vs 41.2 ± 15.6, *P*-value < 0.001) and were more likely to be male (56.5% vs 48.9%) and have any comorbidity. Table 1 summarizes the characteristics of study subjects for selected variables.

Table 1
Characteristics of the study sample for selected variables, Mexico 2021

Characteristic	COVID-19 pneumonia				*p*
	No (n = 45,337)		Yes (n = 1,661)		
Gender					
Female	23,170	(51.1)	723	(43.5)	< 0.001
Male	22,167	(48.9)	938	(56.5)	
Age (years), mean ± SD	41.2 ± 15.6		61.9 ± 15.0		< 0.001
Age group (years)					
18–27	9,404	(20.7)	27	(1.6)	< 0.001
28–33	8,833	(19.5)	47	(2.8)	
35–42	8,890	(19.6)	111	(6.7)	
43–54	9,112	(20.1)	299	(18.0)	
55 or above	9,098	(20.1)	1,177	(70.9)	
Previous SARS-COV-2 symptomatic infection					
No	45,222	(99.8)	1,658	(99.8)	0.559
Yes	115	(0.2)	3	(0.2)	
COVID-19 vaccinated [a]					
No	43,830	(96.7)	1,619	(97.5)	0.075
Yes	1,507	(3.3)	42	(2.5)	
Administered vaccine [b]					
AZD1222 Covishield	593	(39.4)	10	(23.8)	< 0.001
BNT162b2	532	(35.3)	15	(35.7)	
Ad5-nCoV Covidecia	173	(11.5)	4	(9.5)	
CoronaVac	72	(4.8)	0	(0)	
Other	11	(0.7)	1	(2.4)	
Unknown	126	(8.4)	12	(28.6)	
Personal history of:					
Tobacco use (current)					
No	42,171	(93.0)	1,430	(86.1)	< 0.001
Yes	3,166	(7.0)	231	(13.9)	
Asthma					
No	44,266	(97.6)	1,620	(97.5)	0.780
Yes	1,071	(2.4)	41	(2.5)	
Type 2 diabetes mellitus					
No	40,262	(88.8)	974	(58.6)	< 0.001
Yes	5,075	(11.2)	687	(41.4)	
Immunosuppression [c]					
No	44,992	(99.2)	1,610	(96.9)	< 0.001
Yes	345	(0.8)	51	(3.1)	

Abbreviations: **COVID-19**, Coronavirus disease 2019; **SD**, Standard deviation; **SARS-COV-2**, Severe acute respiratory syndrome coronavirus 2.
Notes: 1) The absolute (n) and relative (%) frequencies are presented except if the arithmetic mean ± standard deviation is specified; 2) The *p*-value of ji-squared or t-tests are presented as corresponding.
[a] The vaccinated subjects were those with 2 shots of any COVID-19 vaccine or a single shot (any COVID-19 vaccine) at 15 or more days before illness onset.
[b] Restricted to 1,549 participants that were classified as COVID-19 vaccinated.
[c] Immunosuppression referred to any cause of the related deficiency except for type 2 diabetes mellitus or renal impairment.

Table 2
Predictors of COVID-19, Mexico 2021

Characteristic	RR (95% CI), *p*					
	Bivariate analysis			Multiple analysis		
Gender						
Female	1.000					
Male	1.010	1.007–1.014	< 0.001	1.007	1.004–1.011	< 0.001
Age group (years)						
18–27	1.000			1.000		
28–33	1.002	0.997–1.008	0.360	1.002	0.997–1.007	0.522
35–42	1.010	1.004–1.015	< 0.001	1.008	1.002–1.013	0.004
43–54	1.029	1.024–1.035	< 0.001	1.023	1.018–1.029	< 0.001
55 or above	1.118	1.113–1.124	< 0.001	1.098	1.092–1.104	< 0.001
Previous SARS-COV-2 symptomatic infection						
No	1.000			1.000		
Yes	0.990	0.958–1.024	0.559	1.001	0.969–1.034	0.961
COVID-19 vaccinated [a]						
No	1.000			1.000		
Yes	0.992	0.982–1.001	0.075	0.974	0.965–0.983	< 0.001
Personal history of:						
Tobacco use (current)						
No	1.000			1.000		
Yes	1.036	1.029–1.043	< 0.001	1.025	1.019–1.032	< 0.001
Type 2 diabetes mellitus						
No	1.000			1.000		
Yes	1.100	1.095–1.106	< 0.001	1.052	1.047–1.058	< 0.001
Immunosuppression [b]						
No	1.000			1.000		
Yes	1.099	1.079–1.119	< 0.001	1.067	1.048–1.086	< 0.001

Abbreviations: **RR**, Risk ratio; **CI**, Confidence interval; **COVID-19**, Coronavirus disease 2019; **SARS-COV-2**, Severe acute respiratory syndrome coronavirus 2.
Notes: 1) Generalized linear regression models were used to obtain RR and 95% CI; 2) Multiple regression coefficients were adjusted by variables listed in the table.
[a] The vaccinated subjects were those with 2 shots of any COVID-19 vaccine or a single shot (any COVID-19 vaccine) at 15 or more days before illness onset.
[b] Immunosuppression referred to any cause of the related deficiency except for type 2 diabetes mellitus or renal impairment.

In multiple analysis (Table 2) and after adjustment by a history of symptomatic COVID-19 and other comorbidities, vaccinated subjects were at decreased risk of developing pneumonia (RR = 0.974, 95% CI 0.965–0.983). The association of having a previous COVID-19 episode was not significant (RR = 1.001, 95% CI 0.969–1.034). The interaction between vaccination and reinfection status was not significant (*P*-value = 0.846).

Discussion

The results from our observational study suggest that COVID-19 vaccines provide better protection against pneumonia than previous symptomatic infections. Our results also highlight the relevance of offering vaccination to all eligible subjects despite a previous symptomatic SARS-CoV-2 infection.

By January 2022 and according to official data of the government of Mexico, 82 million Mexicans (64% of the total population of the country) had been fully vaccinated against COVID-19. The AZD1222 Covishield (AstraZeneca) or BNT162b2 (Pfizer, Inc./BioNTech) vaccines had been administered to around 7 of 10 immunized subjects.

In our study and as presented in Supplementary Data 2, adults integrating the vaccinated group were older than those from the reinfection group (49.9 ± 14.6 vs 40.1 ± 11.7 years, *P*-value < 0.001). In consequence to the highest mean age, type 2 diabetes mellitus was frequent (18.3% vs 11.0%, *P*-value= 0.045). The COVID-19 strategy vaccination, where older subjects were prioritized, might be determining the observed differences.

Previously published data suggest that unvaccinated patients with COVID-19 who recovered from severe illness are at increased risk of developing pneumonia after reinfection (Murillo-Zamora et al., 2021). This may be secondary to the persistence of factors conditioning severe manifestations and support the benefit of vaccinating to all eligible adults.

After a natural infection, the length of immunity under endemic conditions is above 90 days (Townsend et al., 2021). However, and against the emergence of variants of concern, the protective effect of circulating antibodies from recovered patients who had COVID-19 might be weak (Planas et al., 2021).

The limitations of our study must be cited. First, no serologic data were collected and therefore, only symptomatic infections were evaluated. Second, we lacked genomic data to ensure that second-time infections were reinfections. However, in our study sample, the mean elapsed days between illness episodes were about six months (175 ± 64 days), which might discard itself a large proportion of persistent SARS-CoV-2 infections (Vibholm et al., 2021). In vaccinated adults, the mean days between the last shot and illness onset were 69 ± 47 days. Third, and as cited previously, the interval between episodes in reinfection cases was longer (*P*-value < 0.001) than the period from the last vaccine shot to illness onset in vaccinated individuals. As antibodies titers may wane with time (Gaebler et al., 2021), these differences might have an impact on the presented results. Finally, we were unable to identify specific pathogenic variants or disease severity of the first episode to obtain stratified estimates of interest.

Conclusions

The COVID-19 vaccines provide better protection against pneumonia than previous symptomatic infection. Therefore, offering immunization to all eligible subjects despite the presence of a previous symptomatic episode of SARS-CoV-2 infection might be useful to reduce the social and economic burden of the COVID-19 pandemic.

Declaration of competing interests

The authors have no competing interests to declare.

Authors' contributions

EMZ conceived and designed the experiments and also wrote the first draft of the manuscript; XT and JGE did data analysis and data collection; MH and VBG contributed to the methodology and writing—review and editing; MRS, MROC, and JAGS contributed with revisions and data analysis; and OMC performed the experiments, analyzed the data, and is responsible for the final version of the manuscript that has been read and approved by all authors.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Ethics approval and consent to participate

This study was approved by the Local Health Research Committee of the Mexican Institute of Social Security (approval R-601-2020-015).

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