

Increased risk of hospitalization and death in Mexican children and adolescents with COVID-19 and comorbidities

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Abstract

Background: Although COVID-19 (coronavirus disease 2019) in children is usually mild, they need hospitalization and intensive care in exceptional cases. Adverse outcomes have been observed mainly among children with comorbidities, justifying their vaccination. This study aimed to assess the risk of hospitalization and death in Mexican children and adolescents with COVID-19 and comorbidities. **Methods:** A cross-sectional study was performed on 366,542 confirmed COVID-19 cases under 18 years, reported by the Mexican Ministry of Health up to July 9, 2022. Logistic regression models were performed. **Results:** The mean age was 10.98 years, 50.6% were male, and 73% reported at least one comorbidity. The percentage of hospitalization and death in COVID-19 patients with and without comorbidities was 3.52%, and 0.20%, respectively; children with comorbidities presented a higher percentage of hospitalization (14.0%) and death (1.9%). The probability of hospitalization was 5.6 times greater in pediatric patients with COVID-19 and comorbidities, and the comorbidities that showed the greatest risk were immunosuppression (odds ratio (OR) 22.06), chronic kidney disease (CKD) (11.36), and cardiovascular diseases (5.66). The probability of death in patients with comorbidities was 11.01 times higher than in those without diseases, and the highest risk was observed in those with CKD (OR 12.57), cardiovascular diseases (6.87), and diabetes (5.83). **Conclusions:** Pediatric patients with comorbidities presented a higher risk of severe COVID-19. It is suggested that vaccination should be promoted with greater emphasis on pediatric patients with comorbidities.

Keywords: COVID-19. SARS-CoV-2. Comorbidities. Pediatrics. Hospitalization. Death.

Riesgo incrementado de hospitalización y muerte en niños y adolescentes mexicanos con COVID-19 y comorbilidad

Resumen

Introducción: Aunque COVID-19 (enfermedad por coronavirus 2019) en niños es usualmente leve, en casos excepcionales requieren hospitalización y cuidados intensivos. Los resultados adversos han sido observados principalmente en los niños

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con comorbilidades, justificando su vacunación. El objetivo de este estudio fue evaluar el riesgo de hospitalización y muerte en niños y adolescentes mexicanos con COVID-19 y comorbilidades. **Métodos:** Estudio transversal en 366,542 casos de COVID-19 confirmados, menores de 18 años y reportados por la Secretaría de Salud de México, hasta el 9 de julio del 2022. Se ejecutaron modelos multivariados de regresión logística. **Resultados:** El promedio de edad fue de 10.98 años, 50.6% de sexo masculino, y 73% reportaron al menos una comorbilidad. El porcentaje de hospitalización y muerte en pacientes con COVID-19 sin comorbilidades fue 3.52% y 0.20%, respectivamente; mientras que los pacientes con comorbilidades presentaron más elevados porcentajes de hospitalización (14.0%) y muerte (1.9%). La probabilidad de hospitalización fue 5.6 veces más en los pacientes con COVID-19 y comorbilidades, comparando con aquellos sin comorbilidades. Las comorbilidades que mostraron más riesgo fueron inmunosupresión (razón de momios (RM) 22.06), enfermedad renal crónica (ERC) (RM 11.36) y enfermedades cardiovasculares (RM 5.66). La probabilidad de muerte en los pacientes con comorbilidades fue 11.01 veces más que en aquellos sin enfermedades, y fue más elevado en aquellos con ERC (RM 12.57), enfermedades cardiovasculares (RM 6.87) y diabetes (RM 5.83). **Conclusiones:** Los pacientes pediátricos con comorbilidades presentaron mayor riesgo de COVID-19 severo, por lo que se sugiere promover con mayor énfasis la vacunación en ellos.

Palabras clave: COVID-19. SARS-CoV-2. Comorbilidad. Pediátricos. Hospitalización. Muerte.

Introduction

Although children and adolescents have a lower risk of infection and severity of coronavirus disease 2019 (COVID-19) compared to adults, in the presence of comorbidities, the risk of developing more severe forms of this disease is higher¹. Studies have shown that some underlying medical conditions such as asthma, immunosuppression, Type 1 diabetes, obesity, cardiovascular disease, congenital circulatory anomalies, neurodevelopmental disorders, anxiety or fear-related disorders, and depressive disorders have been related to an increased rate of fatal health outcomes^{2,3}.

Some studies have reported a low incidence of COVID-19 in children and adolescents around the world: from the total cases of COVID-19, the World Health Organization estimated that 8.5% were children aged under 18 years⁴, UNICEF reported that 21% of cases occurred in individuals under 20 years⁵, and a Mexican nationwide study reported that 2% were cases under 15 years⁶.

In Europe, half of the children and adolescents with antibodies against SARS-CoV-2 have experienced symptoms; other studies in Latin America reported that most cases of young people were asymptomatic⁷. Hospitalization due to severe COVID-19 disease in children is rare, and the respiratory symptoms of these inpatients are more apparent than in infected children in the community. Fatality cases in hospitalized children are relatively low at 1%, compared to 27% across all other age groups⁸. Another study reported that < 5% of affected individuals are known to be children and <1% of those required ventilatory support⁹.

Scientific evidence has shown that most children with SARS-CoV-2 infection have been asymptomatic or had mild COVID-19 symptoms, and few children are at risk of severe COVID-19; however, some children with comorbidities have had a severe illness and have shown a higher risk of death¹⁰. Although COVID-19 in children is usually mild, in exceptional cases, they can become seriously ill and need hospitalization and intensive care. One adverse outcome has been termed multisystem inflammatory syndrome in children (MIS-C), characterized by fever, severe inflammation, and multisystem disorders, causing approximately 1–2% of overall mortality¹¹. These adverse outcomes have been observed mainly among children with comorbidities. This study aimed to assess the risk of hospitalization and death in children and adolescents with COVID-19 and comorbidities living in Mexico.

Methods

Databases and data extraction

This is a cross-sectional study carried out from the laboratory-confirmed COVID-19 cases reported by the Federal Ministry of Health in Mexico (MoH) through the anonymized and open-access COVID-19 database published by the Epidemiological Surveillance System for Viral Respiratory Diseases¹².

As of July 9, 2022, the MoH database registered 370,947 laboratory-confirmed cases of COVID-19 in people under 18 years of age, 4405 records with missing or unknown comorbidity or condition were excluded from the study. The following variables were extracted and assessed: sociodemographics, modifiable risk

factors, and other health conditions such as smoking and obesity, and diagnosis of non-communicable diseases (NCD): asthma, cardiovascular disease, chronic kidney disease (CKD), diabetes Type 1 and 2, hypertension, and immunosuppression. The main outcomes considered were the type of health care received (out-patient care vs. hospitalization) and death. The descriptors in the database did not define the classification method for comorbidities. The information was obtained through a dichotomous questionnaire that the pollster filled out with the information provided by the patient. Finally, the death variable was analyzed using the date of death.

This study did not require ethical review since it is based on open, anonymized data from the Mexican MoH. The database can be consulted at the following link: <https://datos.gob.mx/busca/dataset/informacion-referente-a-casos-covid-19-en-mexico12>.

Statistical analysis

Continuous variables were described using measures of central tendency. Categorical variables were described as percentages. The prevalence of COVID-19 cases without and with comorbidities was estimated from a specific population of interest: COVID-19 cases without comorbidities ($n = 339,780$), then multiplied by 100 and divided by the overall population ($n = 366,542$). Then, χ^2 test was performed to compare the percentages of patients with and without NCDs or modifiable risk factors between health outcomes of interest: hospitalization or death from COVID-19.

The likelihood of being hospitalized or death was assessed according to NCDs and to modifiable risk factors, estimating odds ratios (ORs) with 95% confidence intervals and their corresponding p values, using a multivariate logistic regression model adjusted by age, sex, and for each one of the comorbidities and risk factors analyzed. All statistical analysis was performed using Stata SE version 15.0 software (Stata Corporation, College Station, TX, USA).

Results

From the total 6,303,932 COVID-19 cases accumulated until July 9, 2022, the percentage of pediatric cases under 18 years was 6% ($n = 366,542$ analyzed in this study) and the average age was 10.98 years. **Table 1** shows the general characteristics of Mexican children with COVID-19. From the total number of cases analyzed, the average age was 10.98 years, and

50.66% of the cases were males and most cases (54.57%) were reported by the MoH providers caring for the uninsured, followed by providers of the Mexican Institute of Social Security (IMSS, for its Spanish acronym) caring for social security beneficiaries (36.33%) (**Table 1**).

Table 2 shows that of the total studied population ($n = 366,542$), most cases had COVID-19 diagnosis only (92.70%), and 7.30% reported at least one comorbidity or risk factor. Regarding cases without comorbidities ($n = 339,780$), most were treated as ambulatory patients (96.50%), only 3.52% were hospitalized, and 0.20% died; in contrast, from the total cases with at least one comorbidity ($n = 26,762$), 86.0% were ambulatory patients, 14.03% were hospitalized, and 1.90% died. Regardless of the presence of comorbidities, the crude percentage of hospitalization was 4.29% (15,729 hospitalized/366,542 infected), and the percentage of death was 0.32% (1,191 deaths/366,542 infected).

Table 2 also shows the percentage of pediatric COVID-19 cases with comorbidities and risk factors across health-care services and the percentage of comorbidities by age groups. From the total cases with at least one comorbidity, the most frequent NCD was asthma (34.0%), followed by immunosuppression (6.48%), diabetes (5.15%), cardiovascular disease (4.83%), hypertension (4.01%), CKD (2.45%), and the most frequent modifiable risk factor was obesity (32.84%). Regarding specific comorbidity and health-care services used, COVID-19 cases with asthma, diabetes, cardiovascular diseases, hypertension, and obesity were significantly more treated as ambulatory cases than hospitalized ($p \leq 0.013$, in all cases); a significantly higher percentage of cases with immunosuppression were hospitalized (57.29%) compared with those treated as ambulatory patients (42.71%) ($p = 0.000$). Furthermore, CKD was the comorbidity with a higher percentage of death (7.61%), followed by cardiovascular disease (6.80%) and immunosuppression (6.63%). When comparing the percentage of death versus hospitalization by comorbidity, all comorbidities showed significantly higher percentages of hospitalization than death ($p = 0.000$).

Concerning the age groups, from the total study population, the group between 12 and 17 years old showed the highest percentage of COVID-19 (54.23%), and cases <5 years presented a higher proportion of hospitalization (14.57%) and death (1.19%) than other age groups (**Table 2**).

Table 3 shows the likelihood of hospitalization or dying among pediatric patients with comorbidities or

Table 1. General characteristics of children and adolescents with COVID-19 in Mexico (July 9, 2022)

Variables	Frequency	%
Total study population	366,542	100
Gender		
Female	180,868	49.34
Male	185,674	50.66
Health services providers		
Ministry of Health	200,031	54.57
Mexican Institute of Social Security, IMSS (for its Spanish acronym)	133,174	36.33
Private healthcare services	19,378	5.29
Institute for Social Security and Services for State Workers, ISSSTE (for its Spanish acronym)	5,087	1.39
Healthcare services for state employees	4,064	1.11
IMSS-Bienestar	1,852	0.51
Mexican Petroleum Company, PEMEX (for its Spanish acronym)	1,276	0.35
Ministry of the Navy, SEMAR (for its Spanish acronym)	482	0.13
Ministry of Defense, SEDENA (for its Spanish acronym)	462	0.13
Municipal government services	429	0.12
National System for the Integral Development of the Family, DIF (for its Spanish acronym)	138	0.04
University healthcare services	105	0.03
Red Cross	44	0.01
Not specified	20	0.01

risk factors compared to those without comorbidities. Pediatric patients with COVID-19 and NCD comorbidities had 5.65 times greater risk of hospitalization than those without any NCD diagnosis or no risk factors. Immunosuppression is the NCD that poses the greatest hospitalization risk (OR 22.06), followed by CKD (OR 11.36), cardiovascular disease (OR 5.66), and diabetes (OR 4.51). Patients with obesity also had a greater risk of hospitalization of 2.15. Regarding mortality risk, pediatric patients with NCDs and modifiable risk factors presented 11.01 times higher likelihood of death than those without comorbidities. The highest risk was observed in the case of CKD (OR 12.57), followed by cardiovascular disease (OR 6.87) and diabetes (OR 5.83), while asthma was found to be a significant protective factor against death (OR 0.50). Further, considering the odds of hospitalization and death by age groups: COVID-19 cases lower than 5 years old showed significantly higher probabilities of hospitalization (OR 5.45) or death (OR 7.63) than those between 5 and 11 years old. However, the age group between 12 and 17 years old showed a significantly lower probability of hospitalization (OR 0.66) and slightly and non-significant higher odds of death than cases between 5 and 11 years (1.10; $p = 0.271$).

Table 4 shows the odds of hospitalization in COVID-19 patients with comorbidities or modifiable risk factors by age group. In the group of patients under 5 years old, those with underlying comorbidity had an overall 4.59 times likelihood of hospitalization greater than

those without comorbidities, and considering the odds by each comorbidity, the highest risk for hospitalization was observed for immunosuppression (OR 13.41) and cardiovascular disease (OR 6.52); patients between 5 and 11 years had an overall risk of hospitalization of 6.52 higher than those without comorbidities, and the highest risk of hospitalization was observed in patients with immunosuppression (OR 27.03) and CKD (OR 6.12); in the age group between 12 and 17 years, the overall likelihood of hospitalization was 5.70 times greater than in patients without comorbidities, and the highest risk was in immunosuppression (OR 28.27), CKD (OR 16.90), and diabetes (OR 6.71) (Table 4).

Table 5 shows the odds of death in patients with COVID-19 and comorbidities or risk factors by age group. Patients under 5 years had 7.79 times higher overall likelihood of death than those without comorbidities, and this likelihood was higher for cardiovascular diseases (OR 7.09) and CKD (OR 6.75); the group aged between 5 and 11 years had an overall higher risk of death of 14.50-fold risk of death than children without comorbidities, as well children with immunosuppression and CKD had 6.69 and 6.00 times, respectively, higher risk of death; finally, in the group of children between 12 and 17 years their overall risk of death was 11.36 times greater than in those without comorbidities, and the highest risk was observed in CKD (OR 19.57) and immunosuppression (OR 11.42) (Table 5).

Table 2. Percentage of comorbidities and risk factors by healthcare services used among Mexican pediatric patients under 18 years old with COVID-19

	Studied population ambulatory			Hospitalized			Death		
	n = 366,542	Percentage	n = 350,813	Percentage	n = 15,729	Percentage	n = 1,191	Percentage	p-value**
COVID-19, diagnosis only	339,780	92.70 [†]	327,805	96.50 [§]	11,975	3.52 [§]	681	0.20 [§]	0.000
COVID-19 with at least one comorbidity or risk factor	26,762	7.30 [†]	23,008	86.00 [‡]	3,754	14.03 [‡]	510	1.90 [‡]	0.000
Comorbidities									
Asthma	9,097	34.00 [‡]	8,659	95.18 ^{**}	438	4.82 ^{**}	17	1.23 ^{**}	0.019
Immunosuppression	1,735	6.48 [‡]	741	42.71 ^{**}	994	57.29 ^{**}	115	6.63 ^{**}	0.000
Diabetes	1,378	5.15 [‡]	1,107	80.33 ^{**}	271	19.67 ^{**}	49	3.55 ^{**}	0.000
Cardiovascular disease	1,293	4.83 [‡]	876	67.75 ^{**}	417	32.25 ^{**}	88	6.80 ^{**}	0.000
Hypertension	1,074	4.01 [‡]	885	82.40 ^{**}	189	17.60 ^{**}	45	4.19 ^{**}	0.000
CKD	657	2.45 [‡]	420	63.93 ^{**}	237	36.07 ^{**}	50	7.61 ^{**}	0.000
Risk factors									
Obesity	8,789	32.84 [‡]	8,190	93.18 ^{**}	599	6.81 ^{**}	84	0.96 ^{**}	0.000
Age groups									
< 5 years	50,082	13.66 [†]	42,786	85.43 [‡]	7,296	14.57 [‡]	594	1.19 [‡]	0.000
5-11 years	117,689	32.11 [†]	113,850	96.74 [‡]	3,839	3.26 [‡]	196	0.17 [‡]	0.000
12-17 years	198,771	54.23 [†]	194,177	97.69 [‡]	4,594	2.31 [‡]	401	0.20 [‡]	0.000

p-value was estimated by means of Chi-squared test, comparing the percentage of COVID-19 patients (with and without comorbidities) regarding healthcare services use: ambulatory versus hospitalization manage, and hospitalization versus death**.

[†]Percentages were estimated from all COVID-19 cases, without and with comorbidities (n = 366,542).

[‡]Percentages were estimated from COVID-19 cases without comorbidities (n = 339,780).

[§]Percentages were estimated from COVID-19 cases with comorbidities (n = 26,762).

**Percentages were estimated from study population with a specific comorbidity: asthma (n = 9,097), immunosuppression (n = 1,735), diabetes (n = 1,378), cardiovascular disease (n = 1,293), hypertension (n = 1,074), CKD (n = 657), or obesity (n = 8,789). ^{††}Percentages were estimated from COVID-19 cases of each age group: <5 years (n = 50,082), 5-11 years (n = 117,689), or 12-17 years (n = 198,771). Some COVID-19 cases used more than one service, for this reason the frequencies in the first column (left) do not correspond exactly to the addition of the second column (ambulatory), third column (hospitalized), and fourth column (dead), CKD: chronic kidney disease.

Table 3. Adjusted odds ratios of hospitalization and death in pediatric patients with COVID-19

Comorbidity/health condition	Risk of hospitalization			Death		
	Adjusted odds ratio	95% CI	p-value	Adjusted odds ratio	95% CI	p-value
At least one comorbidity/risk factor*	5.65	5.42-5.89	0.000	11.01	9.80-12.37	0.000
Comorbidities*						
Immunosuppression	22.06	19.692-24.72	0.000	5.78	4.54-7.36	0.000
CKD	11.36	9.29-13.88	0.000	12.57	8.69-18.18	0.000
Cardiovascular disease	5.66	4.90-6.55	0.000	6.87	5.23-9.03	0.000
Diabetes	4.51	3.82-5.33	0.000	5.83	4.05-8.40	0.000
Asthma	1.30	1.17-1.45	0.000	0.50	0.29-0.85	0.010
Hypertension	1.06	0.85-1.32	0.583	1.80	1.19-2.74	0.006
Risk factors*						
Obesity	2.15	1.95-2.36	0.000	3.17	2.46-4.07	0.000
Age groups						
< 5 years**	5.45	5.23-5.69	0.000	7.63	6.49-8.98	0.000
5-11 years (Reference group)	1	-	-	1	-	-
12-17 years**	0.66	0.63-0.69	0.000	1.10	0.93-1.31	0.271

*Odds ratio in COVID-19 patients with at least one comorbidity or by each comorbidity/risk factor were compared to COVID-19 patients without comorbidities, and adjusted by sex and age.

**Odds ratio in COVID-19 patients of age group < 5 years and age group between 12 and 17 years were compared to patients of age group between 5 and 11 years old. Odds ratio were adjusted by sex and comorbidities. CKD: chronic kidney disease, CI: confidence interval.

Discussion

This study highlights that the percentage of total accumulated COVID-19 cases under 18 years old was 6%. From the total of this population, more than seven of each hundred cases also reported at least one comorbidity and presented a risk of hospitalization and death close to six-fold and over 11-fold, respectively, compared with cases without comorbidities. Immunosuppression, CKD, cardiovascular diseases, and diabetes were comorbidities that significantly increased the risk of hospitalization and death, and obesity was a modifiable risk factor that also increased the risk of severity of COVID-19. Moreover, considering the odds of hospitalization and death by age groups (Tables 4 and 5, respectively), the COVID-19 cases between 5 and 11 years old that reported at least one comorbidity showed the greatest risk of both outcomes of interest.

The Mexican pediatric population studied here showed a lower percentage of COVID-19 than other pediatric populations worldwide. The WHO data suggests that children under 18 years old represent 8.5% of the total COVID-19 cases in the world⁴, UNICEF by July 2022 showed that from a total of confirmed cases of COVID-19 reported by 102 countries, 21% happened in patients under 20 years old⁵. In contrast, our pediatric population showed higher percentages of COVID-19 than other countries: in China, the percentage of

laboratory-confirmed cases among children under 19 years of age was of 2%¹³; in England, between January to May 2020, pediatric cases under 16 years old were 4%¹⁴; in Italy, by March 2020, only 1% were children under 18 years of age¹⁵. Another Mexican nationwide study, updated in October 2020, also studied the pediatric population under 15 years old independently of comorbidities. This study showed a lower prevalence of COVID-19 (2%) but a higher prevalence of hospitalization and death (13.5% and 1.4%, respectively)⁶.

Other countries have reported higher percentages of COVID-19 than our pediatric population: in Canada, by July 2022, among the population of children between 0 and 11 years old, the percentage of them with COVID-19 was 10.5%, and among those between 12 and 19 years was of 8.4%¹⁶; in the United States, between March 2020 and June 2022, among the population under 18 years old, the percentage with COVID-19 was of 15.5%¹⁷; further, from March to December 2020, from a total of laboratory-confirmed cases of COVID-19 among population between 0 and 24 years old: 57.4% of cases occurred in young adults aged from 18 to 24 years old, 7.4% in preschoolers (0-4 years), 10.9% in elementary school (5-10 years), 7.9% in middle school (11-13 years), and 16.4% in high school (14-17 years)¹⁸.

Regarding severity and fatality health outcomes related to COVID-19 among children and adolescents,

Table 4. Risk of hospitalization in patients with COVID-19 and preexistence of comorbidity by age groups

Age group	COVID-19 only (n = 174,042)	At least one comorbidity	Immunosuppression	CKD	Cardiovascular disease	Diabetes	Asthma	Hypertension	Obesity
	OR	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)
< 5 years	1.00	4.59 (4.23-4.99; 0.000)	13.41 (10.39-17.30; 0.000)	3.22 (1.79-5.78; 0.000)	6.52 (5.18-8.21; 0.000)	1.21 (0.85-1.71; 0.285)	1.73 (1.34-2.22; 0.000)	1.03 (0.75-1.41; 0.850)	0.66 (0.49-0.89; 0.007)
5-11 years	1.00	6.52 (6.04-7.03; 0.000)	27.03 (22.57-32.38; 0.000)	6.12 (4.00-9.35; 0.000)	4.68 (3.41-6.43; 0.000)	5.94 (4.26-8.27; 0.000)	1.85 (1.57-2.18; 0.000)	0.84 (0.46-1.55; 0.580)	1.94 (1.59-2.36; 0.000)
12-17 years	1.00	5.70 (5.35-6.08; 0.000)	28.27 (23.86-33.49; 0.000)	16.90 (13.33-21.43; 0.000)	4.21 (3.18-5.57; 0.000)	6.71 (5.44-8.26; 0.000)	1.09 (0.92-1.29; 0.330)	1.20 (0.87-1.67; 0.271)	2.55 (2.27-2.87; 0.000)

Odds ratio were compared to the COVID-19 patients without NCDs comorbidities, adjusted by sex and age, COVID-19 diagnosis only was the category of comparison. CKD: chronic kidney disease, OR: odds ratio.

Table 5. Risk of death in patients with COVID-19 and preexistence of comorbidity by age groups

Age group	COVID-19 only (n = 174,042)	At least one comorbidity	Immunosuppression	CKD	Cardiovascular disease	Diabetes	Asthma	Hypertension	Obesity
	OR	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)	OR (95% CI; p-value)
< 5 years	1.00	7.79 (6.53-9.28; 0.000)	2.82 (1.82-4.37; 0.000)	6.75 (2.77-16.44; 0.000)	7.09 (5.12-9.81; 0.000)	2.79 (1.57-4.95; 0.000)	0.59 (0.19-1.90; 0.384)	2.80 (1.67-4.69; 0.000)	0.81 (0.41-1.62; 0.556)
5-11 years	1.00	14.50 (10.93-19.23; 0.000)	6.69 (4.11-10.89; 0.000)	6.00 (2.37-15.21; 0.000)	2.56 (0.93-7.02; 0.069)	4.39 (1.51-12.76; 0.007)	0.62 (0.22-1.71; 0.354)	2.63 (0.79-8.80; 0.117)	3.28 (1.82-5.91; 0.000)
12-17 years	1.00	11.36 (9.33-13.83; 0.000)	11.42 (7.92-16.46; 0.000)	19.57 (12.56-30.49; 0.000)	5.70 (3.21-10.11; 0.000)	8.35 (5.13-13.59; 0.000)	0.57 (0.29-1.15; 0.118)	0.54 (0.25-1.21; 0.139)	3.82 (2.82-5.18; 0.000)

Odds ratio were compared to the COVID-19 patients without NCDs comorbidities, adjusted by sex and age, COVID-19 diagnosis only was the category of comparison. CKD: chronic kidney disease, NCD: non-communicable disease, OR: odds ratio.

our findings are similar to other worldwide reports. By July 2022, UNICEF reported that, of the total deaths in 90 countries, 0.40% were in children and adolescents under 20 years⁵. In the United States, by December 2020, from a total of pediatric COVID-19 cases, 11.7% were hospitalized, and 3.6% presented severe illness¹. In the international network cohort using European primary care records (France, Germany, and Spain), South Korean and US claims, and hospital databases between January and June 2020 among children and adolescents under 18 years old: from the total diagnosed cases, 4% were hospitalized¹⁹. In a US cohort of pediatric patients under 19 years old, 11.7% were hospitalized for COVID-19, and 31.1% experienced severe COVID-19, showing that patients with one or more chronic conditions presented 3.27 times higher risk of severe COVID-19 than those with none¹. In a Mexican report from February 2020 to March 2021, the proportion of case fatality was below 0.3% in the population between 1 and 20 years old and 2.2% in infants under 1-year old¹⁰. Moreover, our results are inconsistent with what is reported in the scientific literature regarding the fact that the age group from 5 to 11 years old showed the highest probabilities of hospitalization and death than those cases under 5 years or those between 12 and 17 years old.

Regarding the comorbidities that most raised the risk of severity by COVID-19 among our Mexican pediatric population: asthma was the most prevalent comorbidity (34%); although immunosuppression was only prevalent in 6.48% of COVID-19 cases, this disease increased the risk of hospitalization by 22.06 times, and death by 5.78 times, compared to COVID-19 pediatric cases without comorbidities; the second most prevalent disease was obesity (32.84%), which increased the risk of hospitalization by 2.15 times, and death by 3.17 times; moreover, our findings also highlight that after immunosuppression: CKD, cardiovascular disease, and diabetes were the diseases that most increased the risk of hospitalization and death. These results are partially consistent with a cross-sectional study done in more than 900 US hospitals that included patients with COVID-19 aged 18 years or younger: 28.7% had underlying medical conditions, asthma being the most common (10.2%), neurodevelopmental disorders (3.9%), anxiety or fear-related disorders (3.2%), depressive disorders (2.8%), and obesity (2.5%). The main risk factors associated with hospitalization were type 1 diabetes (adjusted risk ratio (aRR) of 4.60) and obesity (aRR of 3.07); further, the risk factors for severe COVID-19 were type 1 diabetes (aRR, 2.38) and cardiac and circulatory congenital anomalies

(aRR, 1.72)². In a Mexican study with 1443 pediatric patients under 19 years old, 3.3% were admitted to the intensive care unit, 1.8% required assisted mechanical ventilation, and mortality was of 1.9%, where the main risk factors for mortality were pneumonia (OR of 6.45), intubation (OR of 8.75), immunosuppression (OR of 3.66), and cardiovascular disease (OR of 3.1)³.

In this study, asthma was the most frequent comorbidity, significantly increasing the risk of hospitalization (OR 1.30; 95% confidence interval [CI] 1.17-1.45; $p = 0.000$), but in contrast, this comorbidity was related with a significant reduction in the risk of death (OR 0.50; 95%CI 0.29-0.85; $p = 0.010$). There is concern that asthma is a risk factor for developing severe COVID-19 and increases the risk of death in the pediatric population; however, some systematic reviews and meta-analyses have shown that asthma is not an independent factor that significantly increases the risk of hospitalization, care unit admission, or death in children and adult population^{20,21}. In contrast, other studies have shown that asthma could be a non-statistically significant protective factor in preventing severe COVID-19. This may be explained by the fact that people with asthma receive treatments that favor low production of IFN- α , thus having a protective role of eosinophils in the airway as well as the immunomodulatory properties of inhaled steroids²² and montelukast²³.

Compared with adults, the proportion of COVID-19 cases in the pediatric population has been lower, which could be explained by significant differences in the immune system. Children have a robust innate immune response, being the first-line defense against SARS-CoV-2, with more natural killer cells (NKC). In addition, children have 'trained immunity,' which involves epigenetic reprogramming of innate immune cells, including NKCs, following exposure to certain stimuli, including infections and vaccines, leading to 'memory'^{24,25}. Children also have a higher proportion of lymphocytes and absolute numbers of T and B cells²⁶. Another proposed immunological explanation is that children are less capable of mounting the pro-inflammatory cytokine storm, which plays an important role in the pathogenesis of severe COVID-19 and is responsible for multiorgan failure in critically ill patients²⁶⁻²⁹. In contrast to this theory, other studies have highlighted that hospitalized children with COVID-19 have higher serum levels of IL-17A and IFN- γ but not TNF- α or IL-6; therefore, children are not less prone than adults to develop a cytokine storm and ARDS²⁸.

The transmission of SARS-CoV-2 among children is a major concern. However, early studies suggest that

children, due to their milder symptoms, do not contribute much to the spread of SARS-CoV-2 since the risk of transmission from an asymptomatic individual with SARS-CoV-2 infection is less than the risk from a symptomatic individual³⁰. In Norway, a prospective study showed a minimal transmission of SARS-CoV-2 among children and adults, finding a percentage of transmission of SARS-CoV-2 child-to-child of 0.9% and child-to-adult of 1.7%, supporting that people under 14 years of age are not the main carriers of SARS-CoV-2 transmission³¹. In this regard, a different expression of angiotensin-converting enzyme 2 (ACE2) receptor in children and adults has been proposed as a factor implicated in the reduced transmission and morbidity of SARS-CoV-2 observed at young ages. Furthermore, children have fewer ACE2 receptors in the respiratory tract than adults³², and these are only in the upper respiratory tract; this could explain why young children are less susceptible to SARS-CoV-2 infection³³ and why they present less severe disease than adults³⁴.

Although the proportion of COVID-19 cases in pediatrics is lower than in adults, some infected children can also develop serious complications, such as MIS-C, which cause inflammation of the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs³⁵. Thus, the vaccination of children is also justified as a strategy to reach herd immunity³⁶ and to avoid severe COVID-19. However, although Mexico's MoH has announced the vaccination against SARS-CoV-2 in children and adolescents, the Mexican National Health and Nutrition Survey for COVID-19 showed that the refusal and hesitancy to vaccinate against COVID-19 had been related to age, being more elevated among people of 60 and older (34.4% and 11.7%, respectively). However, these percentages had also been elevated among adolescents between 10 and 19 years (28.2% and 6.7%, respectively)³⁷. The threshold of 65–70% of the population with flock immunity is the prerequisite to ending this pandemic, either through vaccinations or natural infection; however, widely circulating virus variants and vaccination indecision make this threshold challenging to reach. In addition, novel variants with increased transmissibility and enhanced immune evasion changed the herd-immunity calculation. From an epidemiological perspective, unvaccinated children could become the virus shelter when adults achieve immune protection, given that most COVID-19 cases in children are mild and asymptomatic^{36,38}.

The most important limitation of this study is that comorbidities collected in the Mexican COVID-19 surveillance system were also frequent diseases of the

adult population¹², and specific health conditions in pediatric COVID-19 cases were probably underreported. In addition, the prevalence of confirmed COVID-19 cases found in this study could be underestimated since the pediatric population tends to be asymptomatic or shows mild symptoms of the disease³⁴. On the other hand, Mexico has performed few tests to detect SARS-CoV-2: in May 2020, the Organization for Economic Cooperation and Development reported that Mexico only executed 0.6 tests per thousand inhabitants, while other countries performed a greater number of tests, such as Iceland (146.6), Luxembourg (75.8), Lithuania (52.0), Israel (45.4), and Portugal (41.9)³⁹.

In conclusion, although Mexican children and adolescents have presented much lower percentages of SARS-CoV-2 infection and fatality rates than adults, the pediatric population with comorbidities has presented higher percentages of fatality outcomes. Therefore, children and adolescents with comorbidities should be vaccinated to avoid risks and to prevent transmission of SARS-CoV-2 in schools or communities.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Preston LE, Chevinsky JR, Kompaniyets L, Lavery AM, Kimball A, Boehmer TK, et al. Characteristics and disease severity of us children and adolescents diagnosed with COVID-19. *JAMA Netw Open*. 2021;4:e215298.
2. Kompaniyets L, Agathis NT, Nelson JM, Preston LE, Ko JY, Belay B, et al. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open*. 2021;4:e2111182.
3. Rivas-Ruiz R, Roy-García IA, Ureña-Wong KR, Aguilar-Iltuarte F, Vázquez-de Anda GF, Gutiérrez-Castrellón P. Factores asociados a muerte en niños con COVID-19 en México. *Gac Méd Méx*. 2020;156:516-22.

4. World Health Organization. Coronavirus Disease (COVID-19): Schools. Newsroom. Geneva: World Health Organization; 2020. Available from: <https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-schools>
5. UNICEF. COVID-19 Confirmed Cases and Deaths-UNICEF DATA. New York: UNICEF; 2022. p. 1-2. Available from: <https://www.data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard> [Last accessed on 2022 Aug 10].
6. Rivera-Hernandez M, Ferdows NB, Kumar A. The impact of the COVID-19 epidemic on older adults in rural and urban areas in Mexico. *J Gerontol B Psychol Sci Soc Sci.* 2021;76:e268-74.
7. Llaque P. Infección por el nuevo coronavirus 2019 en niños. *Rev Perú Med Exp Salud Pública.* 2020;37:335-40.
8. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with Covid-19 in United Kingdom: prospective multicenter observational cohort study. *BMJ.* 2020;370:m3249.
9. Felsenstein S, Hedrich CM. COVID-19 in children and young people. *Lancet Rheumatol.* 2020;2:e514-6.
10. González-García N, Castilla-Peón MF, Santos FS, Jiménez-Juárez RN, Bustamante ME, Hibert MA, et al. Covid-19 incidence and mortality by age strata and comorbidities in Mexico City: a focus in the pediatric population. *Front Public Health.* 2021;9:738423.
11. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med.* 2020;383:334-46.
12. Secretaría de Salud-Gobierno de México. Datos Abiertos de México-Información referente a casos COVID-19 en México. Mexico City: Secretaría de Salud; 2020. Available from: <https://www.datos.gob.mx/busca/dataset/informacion-referente-a-casos-covid-19-en-mexico>
13. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA.* 2020;323:1239-42.
14. Ladhani SN, Amin-Chowdhury Z, Davies HG, Aiano F, Hayden I, Lacy J, et al. COVID-19 in children: analysis of the first pandemic peak in England. *Arch Dis Child.* 2020;105:1180-5.
15. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. *N Engl J Med.* 2020;383:187-90.
16. Government of Canada. COVID-19 Epidemiology Update. Canada: Government of Canada; 2022. Available from: <https://www.health-infobase.canada.ca/src/data/Covidlive/epidemiological-summary-of-COVID-19-cases-in-canada-canada.ca.pdf> [Last accessed on 2022 Aug 10].
17. Fleming-Dutra KE. COVID-19 Epidemiology in Children Ages 6 Months-4 Years. Atlanta: Centers for Disease Control and Prevention; 2022. Available from: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-17-18/02-COVID-fleming-dutra-508.pdf>
18. Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 trends among persons Aged 0-24 years. *MMWR Morb Mortal Wkly Rep.* 2021;70:88-94.
19. Duarte-Salles T, Vizcaya D, Pistillo A, Casajust P, Sena AG, Lai LY, et al. Thirty-day outcomes of children and adolescents with COVID-19: an international experience. *Pediatrics.* 2021;148:e2020042929.
20. Wang Y, Chen J, Chen W, Liu L, Dong M, Ji J, et al. Does asthma increase the mortality of patients with COVID-19?: a systematic review and meta-analysis. *Int Arch Allergy Immunol.* 2021;182:76-82.
21. Otunla A, Rees K, Dennison P, Hobbs R, Suklan J, Schofield E, et al. Risks of infection, hospital and ICU admission, and death from COVID-19 in people with asthma: systematic review and meta-analyses. *BMJ Evid Based Med.* 2022;27:263-73.
22. Boechat JL, Wandalsen GF, Kuschner FC, Delgado L. COVID-19 and pediatric asthma: clinical and management challenges. *Int J Environ Res Public Health.* 2021;18:1093.
23. Bozek A, Winterstein J. Montelukast's ability to fight COVID-19 infection. *J Asthma.* 2021;58:1348-9.
24. Lau CM, Adams NM, Geary CD, Weizman OE, Rapp M, Pritykin Y, et al. Epigenetic control of innate and adaptive immune memory. *Nat Immunol.* 2018;19:963-72.
25. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol.* 2020;20:375-88.
26. Valiathan R, Ashman M, Asthana D. Effects of ageing on the immune system: infants to elderly. *Scand J Immunol.* 2016;83:255-66.
27. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med.* 2020;8:e46-7.
28. Nye S, Whitley RJ, Kong M. Viral infection in the development and progression of pediatric acute respiratory distress syndrome. *Front Pediatr.* 2016;4:128.
29. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395:1033-4.
30. Corman VM, Rabenau HF, Adams O, Oberle D, Funk MB, Keller-Stanislawski B, et al. SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. *Transfusion.* 2020;60:1119-22.
31. Brandal LT, Ofitserova TS, Meijerink H, Rykkvin R, Lund HM, Hungnes O, et al. Minimal transmission of SARS-CoV-2 from paediatric COVID-19 cases in primary schools, Norway, 2020. *Euro Surveill.* 2021;26:20202011.
32. Lewis D. What new COVID variants mean for schools is not yet clear. *Nature.* 2021;589:503.
33. Davies NG, Klepac P, Liu Y, Prem K, CMMID COVID-19 Working Group, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med.* 2020;26:1205-11.
34. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA.* 2020;323:2427-9.
35. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis.* 2020;20:e276-88.
36. Zou X, Cao B. COVID-19 vaccines for children younger than 12 years: are we ready? *Lancet Infect Dis.* 2021;21:1614-5.
37. Carnalla M, Basto-Abreu A, Stern D, Bautista-Arredondo S, Shamah-Levy T, Alpuche-Aranda CM, et al. Acceptance, refusal and hesitancy of Covid-19 vaccination in Mexico: Ensanut 2020 Covid-19. *Salud Publica Mex.* 2021;63:598-606.
38. Kostoff RN, Calina D, Kanduc D, Briggs MB, Vlachoyiannopoulos P, Svistunov AA, et al. Why are we vaccinating children against COVID-19? *Toxicol Rep.* 2021;8:1665-84.
39. Organization for Economic Cooperation and Development (OECD). Testing for COVID-19: A Way to lift Confinement Restrictions. Paris: OECD; 2020. Available from: https://www.read.oecd-ilibrary.org/view/?ref=129_129658-l62d71r66u&title=testing-for-covid-19-a-way-to-lift-confinement-restrictions