PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for COVID-19 hospitalizations and deaths in Mexican children and adolescents: retrospective cross sectional study.
AUTHORS	Martínez Valdés, Libny; Richardson López Collada, Vesta; CERONIO, LUIS ENRIQUE; Rodríguez Gutiérrez, Ángela; BAUTISTA-MÁRQUEZ, AURORA; Hernandez-Avila, Mauricio

VERSION 1 – REVIEW

REVIEWER	Gutierrez-Castrellon, Pedro Hosp Gen Dr Manuel Gea Gonzalez
REVIEW RETURNED	26-Aug-2021

GENERAL COMMENTS	Relevant proposal. We must be aware what was the definitions used for obesity and diabetes for this pediatric population. It is interesting to note the low prevalence declared of obesity in children 6-17y (212/2,440=8.7%) when we know the around 20% of Mexican children are obese (not considering overweight), BUT at the same time the frequency of diabetes SOUNDS TO HIGH. Can you imagine 82 cases of diabetic kids in 212 obese children (prevalence of 38.6% of diabetes among obese kids¡¡¡). This limitations to use general definition for variables like this in this type of national data base must be declared on LIMITATIONS OF THE STUDY

REVIEWER	Oliveira, E.A UFMG, Pediatrics
REVIEW RETURNED	08-Sep-2021

GENERAL COMMENTS	Comments to the Authors General comments Valdez and cols. present a manuscript entitled “What are the most important risk factors for COVID-19 hospitalizations and deaths in Mexican children? Retrospective analysis” aimed to study is to describe the epidemiological features of COVID-19 in children under 18 years of age in Mexico. The manuscript type is an “original article” with 18 pages, 1 Figure, 4 Tables, and 41 references. The authors reported epidemiological data on pediatric COVID-19 in Mexico based on a nationwide database. Of more than 5 million records in this database 280,854 records corresponded to children under 18 years of age, of which 74,404 had a final classification compatible for SARS CoV-2. (3.5%). According to the dataset, a total of 5,090 (6.8%) cases were hospitalized: 43.7% of children under 1 year of age required hospitalization. Pneumonia

developed in 3.3% of cases and 17.9% of children under one year of age developed pneumonia. The number of deaths was higher in children under one year of age (case fatality 5.33%). The older the age, the fewer the adverse cases. A history of pneumonia, immunosuppression or other comorbidities, as well as age less than one year, confers greater risk of hospitalization (OR 14.16; CI: [13.1012 -15.3008]) or death (OR 10.59; CI: [8.8021 - 12.7451]). The authors concluded that children under one year of age with COVID-19 in Mexico develop severe disease and die more frequently than older children.

I appreciated the opportunity to review this paper from Mexico looking at the nationwide epidemiological and clinical data for COVID-19 infection in children and adolescents. I congrat the authors on the initiative to explore such a relevant topic within the COVID-19 pandemic context, particularly considering the worrisome situation in Latin America. In my view, this is an obviously timely and important study concerning the outcomes of COVID-19 in pediatric age. Nevertheless, the study has many limitations that should be addressed by the authors

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Specific comments

Title

I suggest rephrasing the Title. Suggestion: Risk factors for COVID-19

hospitalizations and deaths in Mexican children and adolescents: a retrospective cohort study.

Introduction.

I suggest rephrasing the aim of the study.

Methods

This section is the most important aspect of a research paper because it provides the information by which the validity of a study is ultimately judged. In this regard, I suggest a major revision of the Methods section. I believe that the inclusion of subdivisions would benefit our understanding of the study. I suggest: Study design, Participants, Covariates (including definitions), Outcomes, Statistical analysis, and Ethical aspects. In my view, a flowchart with cases included and excluded would help clarify some important data of the cohort. The statistical analysis should be detailed and clarified. For instance, I am not sure if a logistic regression analysis was done to investigate the issue of confounding risk factors

Results.

My major concern regarding this section is the question of the age groups. The authors divided the cohort into three groups (<1y, 1-5y, 6-17y). However, it is not

explained in the Methods section why authors divided groups using this age range. I believe that would be much more clinically relevant including three groups taking account of clinical aspects. For instance, the starting age of adolescence has been considered to be 10-year-old (Please, see Sawyer et al. The age of adolescence. Lancet Child Adolesc Health. 2018;2(3):223-228. Therefore, I do suggest that the patients could be re-divided into another three groups using a different age

range (<2 years, 2–9 years, and 10–17 years).

Regarding the clinical outcomes (ICU, death rates, etc), I believe that the inclusion of the statistics for hospitalized cases would be of great clinical interest (Table 1). For instance, Oliveira et al (Lancet Child Adolesc Health, 2021 Aug;5(8):559-568.), in a similar study, reported an overall death rate of 7.6% among hospitalized Brazilian children with higher hazard for infants and

	adolescents. I do believe that these differences should be discussed in the Discussion section. Discussion section This section is relatively well-balanced, but the authors should include a paragraph regarding the limitations of the study and its impact in their findings. As aforementioned, in this very dynamic situation, the authors must update this section, including recent studies (see comments in Results section)

VERSION 1 – AUTHOR RESPONSE

5. Reviewer: 1 Dr. Pedro Gutierrez-Castrellon, Hosp Gen Dr Manuel Gea Gonzalez
Comments to the Author:
Relevant proposal. We must be aware what was the definitions used for obesity and diabetes for this pediatric population. It is interesting to note the low prevalence declared of obesity in children 6-17y (212/2,440=8.7%) when we know the around 20% of Mexican children are obese (not considering overweight), BUT at the same time the frequency of diabetes SOUNDS TO HIGH. Can you imagine 82 cases of diabetic kids in 212 obese children (prevalence of 38.6% of diabetes among obese kids¡¡¡). This limitations to use general definition for variables like this in this type of national data base must be declared on LIMITATIONS OF THE STUDY
R= In the section “Strengths and Limitations” it was described this limitation of the public data base used.

6. Reviewer: 2 Dr. E.A Oliveira, UFMG, UFMG
Comments to the Author:
Comments to the Authors

General comments

Valdez and cols. present a manuscript entitled “What are the most important risk factors for COVID-19 hospitalizations and deaths in Mexican children? Retrospective analysis” aimed to study is to describe the epidemiological features of COVID-19 in children under 18 years of age in Mexico. The manuscript type is an “original article” with 18 pages, 1 Figure, 4 Tables, and 41 references.

The authors reported epidemiological data on pediatric COVID-19 in Mexico based on a nationwide database. Of more than 5 million records in this database 280,854 records corresponded to children under 18 years of age, of which 74,404 had a final classification compatible for SARS CoV-2. (3.5%). According to the dataset, a total of 5,090 (6.8%) cases were hospitalized: 43.7% of children under 1 year of age required hospitalization. Pneumonia developed in 3.3% of cases and 17.9% of children under one year of age developed pneumonia. The number of deaths was higher in children under one year of age (case fatality 5.33%). The older the age, the fewer the adverse cases. A history of pneumonia, immunosuppression or other comorbidities, as well as age less than one year, confers greater risk of hospitalization (OR 14.16; CI: [13.1012 -15.3008]) or death (OR 10.59; CI: [8.8021 - 12.7451]). The authors concluded that children under one year of age with COVID-19 in Mexico develop severe disease and die more frequently than older children.
I appreciated the opportunity to review this paper from Mexico looking at the nationwide epidemiological and clinical data for COVID-19 infection in children and adolescents. I congrat the authors on the initiative to explore such a relevant topic within the COVID-19 pandemic context, particularly considering the worrisome situation in Latin America. In my view, this is an obviously timely and important study concerning the outcomes of COVID-19 in pediatric age. Nevertheless, the study has many limitations that should be addressed by the authors
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Specific comments

a) Title: I suggest rephrasing the Title. Suggestion: Risk factors for COVID-19 hospitalizations and deaths in Mexican children and adolescents: a retrospective cohort study.
R= The suggested title was included.

b) Introduction.
I suggest rephrasing the aim of the study.
R= The aim of the study was rephrased.

c) Methods
This section is the most important aspect of a research paper because it provides the information by which the validity of a study is ultimately judged. In this regard, I suggest a major revision of the Methods section. I believe that the inclusion of subdivisions would benefit our understanding of the study. I suggest: Study design, Participants, Covariates (including definitions), Outcomes, Statistical analysis, and Ethical aspects. In my view, a flowchart with cases included and excluded would help clarify some important data of the cohort. The statistical analysis should be detailed and clarified. For instance, I am not sure if a logistic regression analysis was done to investigate the issue of confounding risk factors
R= The methodology was described with more detail, considering the subdivisions proposed by the reviewer; instead of using a flowchart, we described in the results section the total number of children included in the study, from the total number of registries contained in the national data base.

d) Results.
My major concern regarding this section is the question of the age groups. The authors divided the cohort into three groups (<1y, 1-5y, 6-17y). However, it is not explained in the Methods section why authors divided groups using this age range. I believe that would be much more clinically relevant including three groups taking account of clinical aspects. For instance, the starting age of adolescence has been considered to be 10-year-old (Please, see Sawyer et al. The age of adolescence. Lancet Child Adolesc Health. 2018;2(3):223-228. Therefore, I do suggest that the patients could be re-divided into another three groups using a different age range (<2 years, 2–9 years, and 10–17 years).
R= The study population was divided in 4 groups: children less than one-year-old, children 1 to 5 years old, children 6 to 9 years old, and adolescents (10 to 17 years old). We maintained the group of children less than one-year-old, since the behaviors of the outcomes of interest were very different within this group.

Regarding the clinical outcomes (ICU, death rates, etc), I believe that the inclusion of the statistics for hospitalized cases would be of great clinical interest (Table 1). For instance, Oliveira et al (Lancet Child Adolesc Health, 2021 Aug;5(8):559-568.), in a similar study, reported an overall death rate of 7.6% among hospitalized Brazilian children with higher hazard for infants and adolescents. I do believe that these differences should be discussed in the Discussion section.
R= Specific odds ratios for hospitalization and death were included in table 4, by age group.

Discussion section
This section is relatively well-balanced, but the authors should include a paragraph regarding the limitations of the study and its impact in their findings. As aforementioned, in this very dynamic situation, the authors must update this section, including recent studies (see comments in Results

section)
R= A paragraph with this suggestion was included in the discussion section.

VERSION 2 – REVIEW

REVIEWER	Oliveira, E.A UFMG, Pediatrics
REVIEW RETURNED	04-Jan-2022

GENERAL COMMENTS	No comments