PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Retrospective observational study of the influence of the COVID outbreak on infants' hospitalisation for acute bronchiolitis
AUTHORS	Berdah, Laura; Romain, Anne-Sophie; Rivière, Simon; Schnuriger, Aurélie; Perrier, Marine; Carbajal, Ricardo; Lorrot, Mathie; Guedj, Romain; Corvol, Harriet

VERSION 1 – REVIEW

REVIEWER	Siciliano Nascimento , milena Hospital Israelita Albert Einstein
REVIEW RETURNED	14-Feb-2022

GENERAL COMMENTS	Influence of the COVID outbreak on infants' hospitalization for acute bronchiolitis. bmjopen-2021-059626 The topic about reducing hospitalizations for bronchiolitis or other respiratory diseases during the pandemic in the years 2019/2020 is interesting, however, some other authors have already addressed it and it is no longer unprecedented as it was 1 year ago. It would be very interesting if the authors continued the research showing what happened in 2021 as the restrictive measures of social isolation were more flexible. BACKGROUND The introduction contextualizes the problem but superficially. METHODS Considering that the definition of bronchiolitis is to be an inflammatory disease of a viral origin that affects infants aged 0-2 years, what are the authors' justification for including infants aged 0 to 12 months?Resultados: The total number of hospitalizations described in the results is annual or only the semester (October to March) included in the study. It was not clear because the authors cited average hospitalization 449/year Does your institution use a disease severity score such as the PIM2 (Pediatric Index of Mortality) . If so, it would be interesting to include it in the demographic characterization.

	DISCUSSION Discussion points to interesting topics. For this reason, I reinforce how interesting it would be to complement the results until January 2022. This analysis would bring information that the authors themselves bring to the discussion (lines 47-57) as important future data.

REVIEWER	Curatola, Antonietta University Hospital Agostino Gemelli
REVIEW RETURNED	03-Mar-2022

GENERAL COMMENTS	This study analyses the impact of COVID-19 outbreak on infants' hospitalization for acute bronchiolitis, comparing data obtained during the COVID-19 period with those of the 3 previous years. The study design is well done and the paper is overall clear and well written. However it still several points need to be addressed. ABSTRACT The Abstract is well written. The conclusions could be shortened INTRODUCTION The introduction section is adequately written, providing all necessary information to the readers in a brief and precise manner. Page 4, Lines 19-20: ICU should be written in full at its first mention MATERIAL AND METHODS In the material and methods section, the study design is well written overall. However, some points need to be clarified: 1. Page 6, Lines 7-9: the authors refer to a retrospective study. However, I think that it is a retrospective, observational and cross-sectional study. They should correct this sentence. 2. The inclusion and exclusion criteria are not listed. Please include these in the text 3. Page 6, Lines 24-46: "Three physicians reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form". This section should also implemented including what demographic and clinical data were collected by the physicians (e.g. gender, age, ethnicity, comorbidity, prematurity, etc.). 4. Page 6, Lines 39-50: The statistical analysis section needs to be rewritten. Have you analysed the normality of the distribution for continuous variables with the Shapiro-wilk or Kolmogorov test? Based on these results the authors should present normally distributed continuous variables as mean and standard deviation (SD) and not normally distributed continuous variables as median and interquartile range (IQR). The authors talk about a comparison between two periods, pre-COVID and post-COVID. In this case the tests to be used will be different depending on the variables analysed, i.e. chi-square for categorical variables, two-tailed unpaired Student's t for normally distributed continuous variables and Mann-Whitney test for not normally distributed ones. Clarify these points in the text RESULTS The results of the study are presented concisely and clearly. 1. Tables are appropriate, a legend with abbreviations should be added. 2. It would also be interesting to know the severity of the patient

	(triage code) on arrival in the pediatric emergency department. DISCUSSION The discussion section is well argued, maybe some concepts are a bit redundant. The authors emphasised that not only the outbreak of acute bronchiolitis during the COVID period in French was reduced, but it was also delayed by several weeks. 1. Already last year, several preliminary studies showed a clear reduction in the rate of bronchiolitis admitted to Emergency Department both in France and in other European countries such as Belgium and Italy. These studies should be cited and discussed in the text, underlining the shift of the epidemic peak by a few weeks: ♣ Van Brusselen D, De Troeyer K, Ter Haar E, et al. Bronchiolitis in COVID-19 times: a nearly absent disease?. Eur J Pediatr. 2021;180(6):1969-1973. doi:10.1007/s00431-021-03968-6 ♣ Curatola A, Lazzareschi I, Bersani G, Covino M, Gatto A, Chiaretti A. Impact of COVID-19 outbreak in acute bronchiolitis: Lesson from a tertiary Italian Emergency Department. Pediatr Pulmonol. 2021;56(8):2484-2488. doi:10.1002/ppul.25442 ♣ Guedj R, Lorrot M, Lecarpentier T, Leger PL, Corvol H, Carbajal R. Infant bronchiolitis dramatically reduced during the second French COVID-19 outbreak. Acta Paediatr. 2021;110(4):1297-1299. doi:10.1111/apa.15780 ♣ Di Mattia G, Nenna R, Mancino E, et al. During the COVID-19 pandemic where has respiratory syncytial virus gone?. Pediatr Pulmonol. 2021;56(10):3106-3109. doi:10.1002/ppul.25582 2. Page 11, Lines 5-11: the sentence “In Italy, a recent study showed that the main cost item is related to young infants, in particular, those below 3 months of age, and RSV continues to be the main causative agent of severe bronchiolitis.” lacks reference. 3. Page 11, Lines 17-27: The sentence is a speculation. It can be deleted. In conclusion this is a interesting article, but it needs major revision.

REVIEWER	Comaru, Talitha Farroupilha Federal Institute of Education Science and Technology
REVIEW RETURNED	09-Mar-2022

GENERAL COMMENTS	Do you have made a great job evaluating a temporal trend of bronchilitis in infants pre and post COVID period. However, I have some concerns about your discussion and conclusions. My biggest concern is regarding a certain extrapolation of the conclusions, especially the possible causes of the reduction in hospitalizations. Attributing the delay in the peak of hospitalizations to the end-of-year festivities, without even comparing it with several other studies, seems to me to be quite hasty. I believe that your work would be much better used if you compared the results with other studies, both in relation to the reduction of hospitalizations and the causative pathogens. It would be interesting to investigate whether other studies in different countries report a delay in the peak of hospitalizations for bronchiolitis.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

The topic about reducing hospitalizations for bronchiolitis or other respiratory diseases during the pandemic in the years 2019/2020 is interesting, however, some other authors have already addressed it and it is no longer unprecedented as it was 1 year ago. It would be very interesting if the authors continued the research showing what happened in 2021 as the restrictive measures of social isolation were more flexible.

We agree with the reviewer that the reduction in number of hospitalisations for bronchiolitis during the pandemic in the years 2019/2020 has been addressed by others. As also suggested by reviewer 2 and 3, more of these studies are now referenced and discussed in the revised manuscript (*please see* the response to Reviewer 2, Discussion section, first comment; as well as the response to reviewer 3).

Indeed, as underlined by the editor, our manuscript was submitted a long time before receiving comments, and before the 2021-2022 winter. As such, we do not have data regarding this last winter during which, as highlighted by the reviewer, the restrictive measures of social isolation were indeed more flexible.

Our study is still original, as we report that the outbreak of acute bronchiolitis was not only smaller but also delayed by several weeks; and as we were able to detail the variation in viral epidemiology across the last years, which has been very little described to date.

BACKGROUND

The introduction contextualizes the problem but superficially.

We are sorry that the reviewer thinks that the introduction contextualizes the problem only superficially. We tried to summarize all essential information in the introduction to further develop important topics in the discussion. Moreover, this comment is on opposition with Reviewer 2 who says that "*The introduction section is adequately written, providing all necessary information to the readers in a brief and precise manner.*"

METHODS

Considering that the definition of bronchiolitis is to be an inflammatory disease of a viral origin that affects infants aged 0-2 years, what are the authors' justification for including infants aged 0 to 12 months?

We thank the reviewer for this comment. We restricted the study to children under 1 year of age in order to limit inclusions to only first episodes of bronchiolitis and exclude second (or more) episodes as well as asthma attacks. As suggested by Reviewer 2 (*please see* the response to the second comment of the Material and Methods section), we added in the revised manuscript inclusion and exclusion criteria.

Resultados:

The total number of hospitalizations described in the results is annual or only the semester (October to March) included in the study. It was not clear because the authors cited average hospitalization 449/year

We thank the reviewer for this comment are sorry for this statement that is confusing. Indeed, we report the total number of hospitalizations for only one semester (October to March) that corresponds to autumn/winter seasons in France. Thus, we changed the sentence to: “Over the pre-COVID period, 1,347 infants were hospitalized for bronchiolitis in our hospital, with a mean of 449 infants per winter.”

Does your institution use a disease severity score such as the PIM2 (Pediatric Index of Mortality) . If so, it would be interesting to include it in the demographic characterization.

We are sorry but we do not use this score in our institution.

DISCUSSION

Discussion points to interesting topics. For this reason, I reinforce how interesting it would be to complement the results until January 2022. This analysis would bring information that the authors themselves bring to the discussion (lines 47-57) as important future data.

We are sorry again, but as explained before, we did not collect these data (please see the response to comment 1). Nevertheless, as suggested also by Reviewer 2 and 3, we have enriched the discussion by adding several references, which are now discussed.

Reviewer #2

This study analyses the impact of COVID-19 outbreak on infants’ hospitalization for acute bronchiolitis, comparing data obtained during the COVID-19 period with those of the 3 previous years. The study design is well done and the paper is overall clear and well written. However it still several points need to be addressed.

ABSTRACT

The Abstract is well written. The conclusions could be shortened

As suggested by the reviewer, the conclusions of the Abstract have been shortened.

INTRODUCTION

The introduction section is adequately written, providing all necessary information to the readers in a brief and precise manner.

Page 4, Lines 19-20: ICU should be written in full at its first mention

We are sorry for this omission and we have made the modification.

MATERIAL AND METHODS

In the material and methods section, the study design is well written overall. However, some points need to be clarified:

1. Page 6, Lines 7-9: the authors refer to a retrospective study. However, I think that it is a retrospective, observational and cross-sectional study. They should correct this sentence.

We thank the reviewer for this comment and have made the modification, the text now reads: "*This retrospective, observational and cross-sectional study was conducted in the Paediatric University Hospital Armand Trousseau, Assistance Publique Hôpitaux de Paris (APHP), in Paris (France).*"

2. The inclusion and exclusion criteria are not listed. Please include these in the text

We thank the reviewer for this comment. We have added inclusion and exclusion criteria in the revised manuscript. The text now reads: "*All infants aged less than 12 months-old hospitalised for a first episode of acute bronchiolitis during the autumn/winter seasons (October 1 to March 31) from 2017 to 2021 (i.e., 2017-2018; 2018-2019; 2019-2020; and 2020-2021) were included. Exclusion criteria were age over 12 months-old, a second episode (or more) of bronchiolitis and/or an asthma attack*."

3. Page 6, Lines 24-46: "Three physicians reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form". This section should also implemented including what demographic and clinical data were collected by the physicians (e.g. gender, age, ethnicity, comorbidity, prematurity, etc.).

We thank the reviewer for these comments and have made the required modification, the text now reads: "*The demographic data collected comprised date of birth, gender and underlying conditions such as prematurity, bronchopulmonary dysplasia, intrauterine growth retardation, congenital heart disease, sickle cell disease, and genetic disease. The clinical data collected at the time of the bronchiolitis episode included date, age, weight, results of the PCR in nasopharyngeal swabs or aspirates for virus identification (Allplex™ Respiratory Panel Assays [Seegene], and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit [Diasorin Molecular]), and medical evoution with duration of the hospitalisation, hopitalisation in ICU, respiratory support (oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive ventilation, invasive ventilation, and extracorporeal membrane oxygenation [ECMO]) and nutritional support.*

4. Page 6, Lines 39-50: The statistical analysis section needs to be rewritten. Have you analysed the normality of the distribution for continuous variables with the Shapiro-wilk or Kolmogorov test? Based on these results the authors should present normally distributed continuous variables as mean and standard deviation (SD) and not normally distributed continuous variables as median and interquartile range (IQR). The authors talk about a comparison between two periods, pre-COVID and post-COVID. In this case the tests to be used will be different depending on the variables analysed, i.e. chi-square for categorical variables, two-tailed unpaired Student's t for normally distributed continuous variables and Mann-Whitney test for not normally distributed ones. Clarify these points in the text.

We thank the reviewer for this comment. As suggested, we tested the normality of the distribution for the three continuous variables "age", "weight" and "duration of hospitalization". The hypothesis of normal distribution was rejected for the three variables. Thus, we modified the presentation of those variables by showing their medians and IQR in the table 1. Moreover, we used a Mann-Whitney test

in order to compare those variables between the two periods and modified the P-values for those variables in the Table 1 and in the text of the manuscript.

Finally, we rewrote the statistical analysis section as follow: "*The normality of the distribution for continuous variables was tested using the Shapiro-wilk test and was rejected for each variable. Patients' characteristics were described as medians with interquartile range for continuous variables and percentages for categorical variables. We compared the patients' characteristics between the pre-COVID periods, defined as October 1 to March 31 2017-2018, 2018-2019, and 2019-2020, with those of the COVID period, defined as October 1, 2020 to March 31, 2021, by using a chi-square test for categorical variables and a Mann-Whitney test for continuous variables. The analyses were performed using STATA 14.2.*"

RESULTS

The results of the study are presented concisely and clearly.

1. Tables are appropriate, a legend with abbreviations should be added.

We thank the reviewer for this comment: "ICU" was changed to "Intensive Care unit" in Table 1 and "RSV" to "Respiratory syncytial virus" in table 2.

2. It would also be interesting to know the severity of the patient (triage code) on arrival in the pediatric emergency department.

We are sorry but we do not use a triage score in our institution, so this information was not available.

DISCUSSION

The discussion section is well argued, maybe some concepts are a bit redundant.

The authors emphasised that not only the outbreak of acute bronchiolitis during the COVID period in French was reduced, but it was also delayed by several weeks.

1. Already last year, several preliminary studies showed a clear reduction in the rate of bronchiolitis admitted to Emergency Department both in France and in other European countries such as Belgium and Italy. These studies should be cited and discussed in the text, underlining the shift of the epidemic peak by a few weeks:

- Van Brusselen D, De Troeyer K, Ter Haar E, et al. Bronchiolitis in COVID-19 times: a nearly absent disease?. Eur J Pediatr. 2021;180(6):1969-1973. doi:10.1007/s00431-021-03968-6

- Curatola A, Lazzareschi I, Bersani G, Covino M, Gatto A, Chiaretti A. Impact of COVID-19 outbreak in acute bronchiolitis: Lesson from a tertiary Italian Emergency Department. Pediatr Pulmonol. 2021;56(8):2484-2488. doi:10.1002/ppul.25442

- Guedj R, Lorrot M, Lecarpentier T, Leger PL, Corvol H, Carbajal R. Infant bronchiolitis dramatically reduced during the second French COVID-19 outbreak. Acta Paediatr. 2021;110(4):1297-1299. doi:10.1111/apa.15780

- Di Mattia G, Nenna R, Mancino E, et al. During the COVID-19 pandemic where has respiratory syncytial virus gone?. Pediatr Pulmonol. 2021;56(10):3106-3109. doi:10.1002/ppul.25582

We thank the reviewer for this comment. As underlined by the editor, our manuscript was submitted a long time before receiving comments, before the 2021-2022 winter. Thus, some of these studies were not published at the time the paper was submitted. As suggested by the reviewer, we have enriched the discussion by referencing these studies that are now discussed:

♣ Van Brusselen D et al. (doi:10.1007/s00431-021-03968-6): We have added a sentence in the discussion that says: "*Results similar to ours were reported in Belgium with a dramatic decrease in bronchiolitis hospitalisations and very limited RSV positive as compared to the last three years*." This reference was cited.

♣ Curatola A et al. (doi:10.1002/ppul.25442): We have added a sentence in the discussion that says: "*Several studies reported reductions in the rate of admission to pediatric emergency departments for acute bronchiolitis during the COVID-19 outbreak*". This reference and the following were cited.

♣ Guedj R et al. (doi:10.1111/apa.15780): This study is from our emergency department and was already referenced in the introduction of the paper, which reads: "*We observed a reduction in the visits to the paediatric emergency department of our hospital for bronchiolitis in the autumn 2020*." We also added/discussed this reference along with the previous one in the discussion (please see above for Curatola et al.).

♣ Di Mattia G et al. (doi:10.1002/ppul.25582): We added a sentence at the end of the conclusion acknowledging this paper, which reads: "*The scientific community should nevertheless keep close surveillance of RSV epidemics since, as underlined by Di Mattia et al., the increase of an immunologically naïve population with infants born from mothers who have not reinforced their immunity to RSV, could lead to greater epidemics in the next winters*."

2. Page 11, Lines 5-11: the sentence "In Italy, a recent study showed that the main cost item is related to young infants, in particular, those below 3 months of age, and RSV continues to be the main causative agent of severe bronchiolitis." lacks reference.

We are sorry for this omission. The reference was listed in the following sentence that also refers to this study (Bozzola E et al. *Respiratory Syncytial Virus Bronchiolitis in Infancy: The Acute Hospitalization Cost.* Front Pediatr. 2021 Jan 18;8:594898). We replaced the reference adequately.

3. Page 11, Lines 17-27: The sentence is a speculation. It can be deleted.

We thank the reviewer for this comment. In this paragraph, we discuss the possible repercussions of a decrease number of bronchiolitis in infancy. The first part of the paragraph discusses possible financial consequences. The second part of the paragraph discusses the impact of bronchiolitis on long-term respiratory outcome in children. Thus, this last sentence summarises these two points.

In conclusion this is a interesting article, but it needs major revision.

Reviewer #3

Dear authors

Do you have made a great job evaluating a temporal trend of bronchilitis in infants pre and post COVID period.

However, I have some concerns about your discussion and conclusions.

My biggest concern is regarding a certain extrapolation of the conclusions, especially the possible causes of the reduction in hospitalizations. Attributing the delay in the peak of hospitalizations to the end-of-year festivities, without even comparing it with several other studies, seems to me to be quite hasty. I believe that your work would be much better used if you compared the results with other studies, both in relation to the reduction of hospitalizations and the causative pathogens. It would be interesting to investigate whether other studies in different countries report a delay in the peak of hospitalizations for bronchiolitis.

We thank the reviewer for these comments, which are in agreement with those of reviewer 2 (please also see response to Reviewer 2, Discussion section, first comment). Indeed, as underlined by the editor, our manuscript was submitted a long time before receiving comments, before the 2021-2022 winter. As such, the comparison with other studies was limited, as many were not yet published at the time we submitted the paper. As suggested by this reviewer as well as reviewer 2, we have enriched the discussion by adding several studies from different countries, which are now referenced and discussed.

VERSION 2 – REVIEW

REVIEWER	Siciliano Nascimento , milena Hospital Israelita Albert Einstein
REVIEW RETURNED	22-Apr-2022

GENERAL COMMENTS	Most of the requests made by the reviewers were answered and the work improved a lot. It don't make sense to exclude the second episode of bronchiolitis, since this profile of internal patient often suffers from the circulation of viruses and influences the number of hospitalizations. This point should be better justified and even discussed. Why not include all bronchiolitis? Can't we have patients who are 18 months old in the first episode? How was it raised by the medical record that it was the first episode? The authors cite that RSV infection has long-term repercussions. Wouldn't a second hospitalization be a consequence that? Reviewer 2 have requested that the paragraph on page 11 lines 17 to 27 be removed. I also believe that it is not part of the scope of the article.

REVIEWER	Curatola, Antonietta University Hospital Agostino Gemelli
REVIEW RETURNED	19-Jul-2022

GENERAL COMMENTS	The authors replied satisfactorily to all my comments. In my opinion, the manuscript is thus improved and suitable for publication in this journal

REVIEWER	Comaru, Talitha Farroupilha Federal Institute of Education Science and Technology
REVIEW RETURNED	09-May-2022

GENERAL COMMENTS	You're made a strongly improvement, based on reviewers comments. Congrats. I'm still thinking about how could be interesting to make comparissons between studies, regarding a delay in acute viral bronchiolitis peak post COVID 19. However, studies pointing these results are emerging at this time worldwide. So, I just recommend to keep looking for it, indeed.