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

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<tr>
<td>AUTHORS</td>
<td>Nguyen, Nhung; Tran, Dien; Schindler, Christian; Nguyen, Lien; Probst-Hensch, Nicole; Vu, Lan; Kuenzli, Nino; Perez, Laura</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>David McBride</th>
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<td>University of Otago,</td>
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<td>Dunedin</td>
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<td>New Zealand</td>
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| REVIEW RETURNED     | 26-Dec-2016 |

<table>
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<tr>
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socio-economic status of the three residential locations?

Page 5 line 36, what effect on the data might happen because the location is 'unidentified'?

Page 5 line 42, why did you choose one and 5 night stays?

REVIEWER
Matthew Rubach
Duke University, USA

REVIEW RETURNED
17-Jan-2017

GENERAL COMMENTS

Nguyen et al have presented data that characterizes illnesses for which children are hospitalized or seek emergency in Hanoi. This is relevant to the global health community, and overall I think it is worthy of publication in a peer-reviewed biomedical journal.

Major criticisms:
Asthma diagnosis: In describing respiratory diseases, the authors have asthma as one of the major categories for respiratory disease among children under 5. Even in 2007 (study period inception), the clinical diagnosis of asthma could not be assigned to a child under age 7. Children under 7 admitted for wheezing technically have 'reactive airway disease' or 'bronchospastic airway disease.' I assume that the asthma ICD-10 coding is out of the authors' control. But if possible, the authors should address this either by renaming 'asthma' in children under age 7 to 'reactive airway disease' or explain in the Methods 'that the coding provided in the registry was 'asthma.' Though this diagnosis should be ascribed to children under age 7, we report it here as asthma so as to have fidelity to the diagnostic coding in the registry.'

Preventable disease burden:
From the data presented on the preponderance of gastrointestinal and respiratory disease among children seeking hospital care in Hanoi, the authors conclude that this burden is 'largely preventable.' But the authors have not presented data identifying etiologies of GI disease or etiologies of respiratory disease that are preventable. For instance, while influenza and pneumococcal pneumonia may be preventable via vaccination, RSV, adenovirus and mycoplasma are not readily preventable beyond improved general hygiene. Similarly, rotavirus is preventable, but Salmonella enteritis is not readily preventable. Because the authors have not presented data on the prevalence of rotavirus-mediated disease or pneumococcal-mediated respiratory disease, etc. I think the final conclusion is fully supported by the results presented.
I would recommend that the authors return to their data to generate a revised final conclusion such as 'many of these respiratory and digestive diseases may be preventable. These data show that further work is needed to characterize the etiologies of respiratory disease and digestive disease in Hanoi so that public health interventions can be devised accordingly.'

Minor criticisms:
Table 2: I do not see a unit of time given (obviously it is "days," but this should be stated).
There is a row called 'Factors related to health status.' From the manuscript text and the Table it is not clear to me what this variable means. Suggest that authors provide information in the Table.
caption so that the reader knows what this variable means.

Table 3: the term crude death ‘rate’ is used. Rate implies events within a unit of time. In this case the unit of time is 8 years (2007-2014). Consider renaming to ‘case fatality ratio’ instead of death rate.

Table 4: For Emergency Visits among 15-17 year-olds, there was 1 death (compared to 108 deaths in < 1 year olds). Yet the adolescents had 1.87 increased odds of death compared to children under 1 year of life. This is possible, of course, if the denominator of 15-17 emergency visits was so low that the Case Fatality Ratio of this population was actually high compared to the CFR of < 1 years-old. But overall it seems like an odd finding. Request that the authors review this statistical finding. If the increased odds of death is in fact increased among adolescents, this should be reported in the Results text and commented on in the Discussion.

Care-seeking of adolescents: related to the point above, it would be helpful if the authors could describe in the methods (if possible) what the usual age is for adolescents to transition to adult medical care. In many developing countries, by age 13 children receive their care in adult wards or adult facilities. Reporting the standard in Hanoi would be helpful for readers to decide on the generalizability of the results presented for adolescents (i.e., if most adolescents in Hanoi do not in fact seek care at the children’s hospital, then the results presented for adolescents are less generalizable and/or incomplete and this might require comment in the Discussion).

Figure 2: caption states admission rates for children under 1 year old and children under 5 years. Meanwhile the figures present rates for children under 1 year old and children 1-4 years old. Suggest correction of the caption so that the caption description reflects what is shown in the Figure.

Copy editing: at times the English is sub-standard in terms of punctuation and wavering back and forth between past and present test and other grammatical errors.

REVIEWER
Lien Anh Ha Do
Murdoch Children’s Research Institute, Melbourne, Australia

REVIEW RETURNED
20-Jan-2017

GENERAL COMMENTS
The manuscript described the hospital admission and emergency rates in the National Hospital of Pediatrics (NHP) – the largest referral hospital in North Vietnam and based in Hanoi. The estimation was based on the hospital records during 7 years (2007-2014). Two models were used to evaluate the risk factors of prolonged hospitalization and death. It is not clear about denominators used for the results reported in this manuscript hence this dramatically impacts on the result meanings.

Below are some points requiring more clarifications:
1. Why the authors use two different denominators when they calculate the rate of emergency visit and the hospital admission rate? Please justify.
2. The presentation of analysis results is not clear. p-value of each risk factor is not specified.
3. Denominator is not specified when a % result is reported, this
makes the reading very difficult and confused.

4. The authors don’t mention about how they handled patient information in order to protect patients’ privacy and confidentiality.

Specific comments

1. The numbers (in the text) were not written in a scientific style, such as: 212'216 should be written as 212,216.
2. The authors should describe more details how they performed the quality control (QC) and quality assurance (QA)? It seems only the information about “date” was checked by this QA/AC process.
3. Should the authors detail the causes of emergency visits of their current data, whether burn or other injury is the leading cause in these cases?
4. Should the authors describe the patients flow of NHP? How many in-patients come from other hospitals (which hospital) or from the Emergency Department or they mostly come from the NHP Outpatient Department?
5. Some sentences are not clear or redundant, such as:
   - Line 2: should be re-phrased as “To describe hospital admission and emergency visit rated…..”
   - Line 30: “our analysis is aimed at…” should be rephrased as “Our analysis aims to understand …”
   - Line 32: “we evaluate the number…” should be replaced as “we estimate the rates of “

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author: Reviewer: 1
Reviewer Name: David McBride
Institution and Country: University of Otago, Dunedin, New Zealand
Please state any competing interests: None Declared

Please leave your comments for the authors below

Thank you, I enjoyed reading this paper.

Comment 3: Page 4, line 14: This section may need some revision, as the meaning is not entirely clear: ‘However, these reports still solely present rates of malnutrition, immunization coverage and the absolute number of cases and deaths due to infectious diseases that are preventable with vaccination such as measles, tuberculosis, typhoid fever, diphtheria, or neonatal tetanus’.

   We have revised accordingly

Comment 4: page 4, line 28. Every day, about 2000-3000 children visit the hospital for a health checkup: It would help set the scene better if could be more specific: are these emergency department attendances, or ‘routine’ attendances for outpatient clinics or consultation?

   We now specify as follows:

   According to the annual report of the VNCH, 95% of Hanoi children visited the hospital directly via VNCH’s outpatient department. Only 5% of all patients were transferred from the provincial hospital (Saint-Paul) and other sector hospitals, such as Post Hospital. Only about 10% of hospital admissions went through the emergency rooms, which were severe cases of respiratory, liver or heart failure.

   Scheduled outpatient visits accounted for about 0.05% of all admissions.

Comment 5: Page 5 line 1, it would help the reader if, as above, you say whether all the children present to the ED as the initial step in assessment.

The procedure for hospital patient check-ups was the following: First, the patients underwent a health check at the out-patient department. Second, children with severe diseases got admitted to the hospital, while the others received prescriptive medication and were treated as outpatients. The emergency department saw patients with life-threatening diseases such as severe breathlessness,
liver and heart failure. Therefore, most patients were admitted through the out-patient department whereas only some 10% were hospitalized via the emergency department.

Comment 6: Page 5 line 8, it would help if the paragraph starting at line 23 was presented here.

Given all revisions, we think that the original structure is adequate.

Comment 7: Page 5 line 9, how and by whom was the ICD coding carried out? This is important, as if coded on discharge by a nosologist it is likely to be accurate, if a clinician less so, the latter probability of diagnostic accuracy being dependent on training and seniority. This is however less important with the higher level diagnostic blocks used.

In the Vietnam National Children’s Hospital, ICD codes of the diseases were assigned by medical doctors at the discharge department. All doctors were trained on ICD coding method and were updated annually.

Comment 8: Page 5, line 23. More detail is needed on the denominator data: this is important. The data coming from community health centres may result in bias, which should be discussed in strengths and weaknesses. Which direction could this take?

The staff from the community level of the Hanoi Population and Family Planning Branch (HPFPB) was responsible for collecting the data (immigrants, emigrants, and death and birth cases) from households in each ward. They regularly updated this information and sent it to the community authorities. Therefore, the population (denominator) did not come from the community health centre.

We revised the sentence in the manuscript to clarify this.

Comment 9: Page 5 line 34, can you make any general comment about the socio-economic status of the three residential locations?

There are substantial socio-economic differences between rural and urban participants. As such, children in urban regions often have a higher standard of living and are able to frequently visit the hospital directly (i.e. no transfer from local hospitals). They are also more easily able to self-fund their hospital costs. It is likely that urban children and their families choose the national hospital, as it is known to have good treatment quality and health services. In contrast, children in rural regions live far away from the hospital, have poorer access to medical facilities and often only visit the hospital for severe illness and emergencies.

Comment 10: Page 5 line 36, what effect on the data might happen because the location is “unidentified”?

The term “unidentified” in this paper means the data did not provide the name of district where children lived. Missing information about the place of living occurred randomly in the registry data. To our knowledge, the unidentified location could occur in children living on the boundary between two districts. Because the proportion of missing location were low (1.7%), the study results were not affected by this.

Comment 11: Page 5 line 42, why did you choose one and 5 night stays?

Hospital admission was defined as stay in the hospital of at least one night. The first possible discharge could, thus, happen after the second day of admission (one night). Therefore, we calculated the hazard ratio for one night as the mildest/shortest form of hospitalization. Since most antibiotics are used for at least five days of a therapy, patients often have to stay in the hospital for at least five nights. Therefore, the sixth day is another typical day for discharges. Thus, we also calculated hazard ratios for five nights.

Reviewer: 2
Reviewer Name: Matthew Rubach
Institution and Country: Duke University, USA
Please state any competing interests: None declared

Please leave your comments for the authors below
Nguyen et al have presented data that characterizes illnesses for which children are hospitalized or seek emergency in Hanoi. This is relevant to the global health community, and overall I think it is worthy of publication in a peer-reviewed biomedical journal.

Major criticisms:

Comment 12: Asthma diagnosis: In describing respiratory diseases, the authors have asthma as one of the major categories for respiratory disease among children under 5. Even in 2007 (study period inception), the clinical diagnosis of asthma could not be assigned to a child under age 7. Children under 7 admitted for wheezing technically have 'reactive airway disease' or 'bronchospastic airway disease.' I assume that the asthma ICD-10 coding is out of the authors' control. But if possible, the authors should address this either by renaming 'asthma' in children under age 7 to 'reactive airway disease' or explain in the Methods 'that the coding provided in the registry was 'asthma.' Though this diagnosis should be ascribed to children under age 7, we report it here as asthma so as to have fidelity to the diagnostic coding in the registry.'

We revised the manuscript accordingly (line 22-25 page 5).

… As we reported all data according to the ICD coding scheme used by VNCH, some data should be interpreted with caution. In particular in case of "asthma" among the youngest children, reactive airway disease may be a better diagnostic description then "asthma" which may be inconsistently used by physicians.

Preventable disease burden:

Comment 13: From the data presented on the preponderance of gastrointestinal and respiratory disease among children seeking hospital care in Hanoi, the authors conclude that this burden is 'largely preventable.' But the authors have not presented data identifying etiologies of GI disease or etiologies of respiratory disease that are preventable. For instance, while influenza and pneumococcal pneumonia may be preventable via vaccination, RSV, adenovirus and mycoplasma are not readily preventable beyond improved general hygiene. Similarly, rotavirus is preventable, but Salmonella enteritis is not readily preventable. Because the authors have not presented data on the prevalence of rotavirus-mediated disease or pneumococcal-mediated respiratory disease, etc. I think the final conclusion is fully supported by the results presented.

I would recommend that the authors return to their data to generate a revised final conclusion such as 'many of these respiratory and digestive diseases may be preventable. These data show that further work is needed to characterize the etiologies of respiratory disease and digestive disease in Hanoi so that public health interventions can be devised accordingly.'

I revised the manuscript as the suggestion of reviewer:

As seen in other parts of the world,3 many of these respiratory and digestive diseases could be prevented. The data collected in this study showed that further research is needed to characterize the etiologies of respiratory and digestive diseases in Hanoi. This will provide the basis for targeted public health interventions to reduce this burden.

Reference


Minor criticisms:

Comment 14: Table 2: I do not see a unit of time given (obviously it is "days," but this should be stated).

There is a row called 'Factors related to health status.' From the manuscript text and the Table it is not clear to me what this variable means. Suggest that authors provide information in the Table caption so that the reader knows what this variable means.
We added unit of hospital duration in the table caption. In the table caption we wrote the hospital duration by age group, gender, residential location and disease groups.

Comment 15: Table 3: the term crude death 'rate' is used. Rate implies events within a unit of time. In this case the unit of time is 8 years (2007-2014). Consider renaming to 'case fatality ratio' instead of death rate.

We revised as reviewer suggested

Table 4: For Emergency Visits among 15-17 year-olds, there was 1 death (compared to 108 deaths in < 1 year olds). Yet the adolescents had 1.87 increased odds of death compared to children under 1 year of life. This is possible, of course, if the denominator of 15-17 emergency visits was so low that the Case Fatality Ratio of this population was actually high compared to the CFR of < 1 years-old. But overall it seems like an odd finding. Request that the authors review this statistical finding. If the increased odds of death is in fact increased among adolescents, this should be reported in the Results text and commented on in the Discussion.

The statistical number in the manuscript was corrected. However, as we presented in table 1, the total number of emergency visits were only 15 cases with only one death, thus, the data are not dense enough to interpret this apparently “higher” percentage of death which was also not statistically significant (p>0.05). We revised the discussion accordingly.

(See response for comment 16th)

Comment 16: Care-seeking of adolescents: related to the point above, it would be helpful if the authors could describe in the methods (if possible) what the usual age is for adolescents to transition to adult medical care. In many developing countries, by age 13 children receive their care in adult wards or adult facilities. Reporting the standard in Hanoi would be helpful for readers to decide on the generalizability of the results presented for adolescents (i.e., if most adolescents in Hanoi do not in fact seek care at the children's hospital, then the results presented for adolescents are less generalizable and/or incomplete and this might require comment in the Discussion).

Thank you for the valued comment. We added a paragraph to explain this issue in Discussion in the manuscripts (line 44 page 9).

Given that children above 13 years of age could be transferred to adult health facilities, rather than the VNCH, particularly for in case of injuries or heart diseases. Therefore the total hospitalisation rate among adolescents in the Hanoi region may be underestimated.

Comment 17: Figure 2: caption states admission rates for children under 1 year old and children under 5 years. Meanwhile the figures present rates for children under 1 year old and children 1-4 years old. Suggest correction of the caption so that the caption description reflects what is shown in the Figure.

We revised the captions of the figure

Comment 18: Copy editing: at times the English is sub-standard in terms of punctuation and wavering back and forth between past and present test and other grammatical errors.

We checked and revised

Reviewer: 3
Reviewer Name: Lien Anh Ha Do
Institution and Country: Murdoch Children's Research Institute, Melbourne, Australia
Please state any competing interests: None declared

Please leave your comments for the authors below

Comment 19: The manuscript described the hospital admission and emergency rates in the National
Hospital of Pediatrics (NHP) – the largest referral hospital in North Vietnam and based in Hanoi. The estimation was based on the hospital records during 7 years (2007-2014). Two models were used to evaluate the risk factors of prolonged hospitalization and death. It is not clear about denominators used for the results reported in this manuscript hence this dramatically impacts on the result meanings.

The denominators of each indicator were presented in the methods and footnotes of the table. For example: “Average annual rates of emergency visits per 1000 children were computed by dividing the average annual number of emergency visits (in three years) by the size of the age-sex-specific population of the Hanoi children in 2013” (line 3-5 page 5); Average annual rates of hospital admission per 1000 children were calculated as the average annual number of hospital admissions divided by the Hanoi children population in 2010 (line 8,9 page 5), so on.

Below are some points requiring more clarifications:

Comment 20: Why the authors use two different denominators when they calculate the rate of emergency visit and the hospital admission rate? Please justify.

Data for hospital admissions was collected from 2007-2014. We used the population in 2010 to calculate average annual number of hospital admissions for this period. On the other hand, data from emergency departments has just been merged into the registry since 2012, hence, this data is from 2012-2014. Therefore, we used the population in 2013 as the mid-period population.

Comment 21: The presentation of analysis results is not clear. p-value of each risk factor is not specified.

We revised by adding p-value ranges in the notes table 2 and table 3

Comment 22: Denominator is not specified when a % result is reported, this makes the reading very difficult and confused.

We reported the method to calculate % in the footnote of each table and revised the table accordingly

Comment 23: The authors don’t mention about how they handled patient information in order to protect patients’ privacy and confidentiality.

In line 32-35 page 4 we presented the variables which we obtained from the electronic registry. Among them, we used an anonymized patient identification randomly assigned by the system, with all children’s names removed from the file by the hospital administration prior to handling data for analyses as a priority defined in the ethical and analytical protocol approved by the hospital. Checking of data quality and completeness (QA/QC) was carried out by staff in the administration department of the hospital. As a rule of the department, staffs are responsible for patients’ privacy and confidentiality.

Specific comments

Comment 24: The numbers (in the text) were not written in a scientific style, such as: 212’216 should be written as 212,216.

We revised as the reviewer suggested.

Comment 25: The authors should describe more details how they performed the quality control (QC) and quality assurance (QA)? It seems only the information about “date” was checked by this QA/AC process

In supplemental material, we presented the QA/AC process. In the third stage of our QA/QC when of checking our data with medical hardcopy documents, we did not find any unmatched field between two registry systems relating to name of disease, ICD code, gender, and location. We assumed that the information in the hardcopy is accurate. Thus, we completed QA/QC process.

Comment 26: Should the authors detail the causes of emergency visits of their current data, whether burn or other injury is the leading cause in these cases?

In this paper we focused on the general pattern of emergency visits and hospital admissions. Amongst them, injury (including burn) was the leading cause of emergency visits, particularly in older children. However, this manuscript did not solely focus on the injury. So we did not provide detail
pattern of injury endpoints such as burn or road traffic accident. This description will be presented in the next manuscript.

Comment 27: Should the authors describe the patients flow of NHP? How many in-patients come from other hospitals (which hospital) or from the Emergency Department or they mostly come from the NHP Out-patient Department?
Please see response in comment 4th.

Comment 28: Some sentences are not clear or redundant, such as:
- Line 2: should be re-phrased as “To describe hospital admission and emergency visit rated…..”
- Line 30: “our analysis is aimed at…” should be rephrased as “Our analysis aims to understand …”
- Line 32: “we evaluate the number…” should be replaced as “we estimate the rates of ”
We revised as the reviewer suggested

Additional update:
Since 1 January 2017, The National Hospital of Pediatrics changes its name into Vietnam National Children’s Hospital. Therefore in this paper, we used the new name.
We also updated affiliation for Laura Perez, a co-author in the manuscript. Dr Laura was used to work in Swiss Tropical and Public Health Institute until June 2016.

**VERSION 2 – REVIEW**

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<th>David McBride</th>
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| REVIEW RETURNED     | 31-Mar-2017 |

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<td>2. The denominator data. It would still seem that this comes from 2 sources. 'Mid census' data is entirely appropriate, but I cannot understand where the 2009 census data from the the General Statistics Office fits in. a. I would therefore still like to see an explanatory paragraph about the census techniques. As I understand it, Vietnam has a history of collecting census data, but the 2009 census was the first to be undertaken since 1979. b. Are the quarterly updated censuses based on the 1994 model, and how do the updates contribute to the denominator? c. If there are such frequent updates, then why is annual data not used. In short, although it may not make much difference to the rates, you must provide some explanation.</td>
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| REVIEW RETURNED     | 27-Mar-2017 |


4.1) The diagnostic validity of using 'doctor coded' in contrast to 'nosologist coded' ICD categories. Reviewer #2 raised this in the context of asthma, the response to which partly addresses my concerns. Misclassification may however still occur: a note to this effect would help reassure me.

Dear Dr David McBride

Thank you very much for your comments. ICD code in the medical documents from VNCH was assigned by medical doctors. This was done at the discharge time and based on the results of diagnosis. That means ICD code is consistent with outcome diagnosis. We agree that this is a source of potential misclassification with some cases of clinical asthma not being properly coded as such and possibly other false positive diagnosis of asthma where complications of acute infections could play a primary role. We have no objective information to know in which direction and under what circumstances such biases influenced our data or whether false negative and positive are balanced. Indeed, a likely scenario could be that the bias pattern depends also on age, with diagnosis of asthma among older ages being most likely more precise than in younger age groups. We expanded about this issue on the line 5-8 in page 9.

“We reported all data according to the ICD coding scheme used by VNCH, therefore, some data should be interpreted with caution. In the case of asthma, for example, reactive airway disease may be a better diagnostic description among the youngest children; asthma may be used inconsistently by physicians”

4.2) The denominator data. It would still seem that this comes from 2 sources. 'Mid census' data is entirely appropriate, but I cannot understand where the 2009 census data from the General Statistics Office fits in.

a. I would therefore still like to see an explanatory paragraph about the census techniques. As I understand it, Vietnam has a history of collecting census data, but the 2009 census was the first to be undertaken since 1979.

Thank you for the careful consideration and understanding of the Vietnam situation. Since 1979, Vietnam had four population censuses. The first census was undertaken in 1979, four year after Vietnam was re-unified (1975). The second census was carried out in April, 1989. This was the first time, Vietnam applied the international concepts, design and data collection methodology in the population census. The third census was conducted in 1999 and the fourth census was implemented in April, 2009. The least census has received the technical support from United Nations Population Fund.

Detailed information about the census methods (including recruitment, content, and major findings etc.) has been published online. The revised manuscript briefly refers to this issue:

“Information in the 2009 population census was published else1. In this study, we only used age and gender specific information for the Hanoi population” (line 30-31 page 5).

4.3) Are the quarterly updated censuses based on the 1994 model, and how do the updates contribute to the denominator?

Based on the list of household members from the 2009 population census, collaborators of Hanoi Population and Family Planning Branch reported every three months updated information to the authorities at the community level, including information about immigrants, emigrants, birth and death,
by age and sex. Before 2009, reporting was limited to total data of immigrants, emigrants, births and deaths without stratification by gender and age.

In short, the procedures for population census data updates changed since 2010.

4.4) If there are such frequent updates, then why is annual data not used.
In short, although it may not make much difference to the rates, you must provide some explanation.

This is indeed a misunderstanding as annual rates were conducted based on the annual updates of population data for children under 5 for the years 2009-2014. However, annual rates for 2007-2008 had not been estimated as there was no denominator available for this period of time. In the manuscript we mentioned:

From line 21- 25 page 5

“To illustrate trends in the annual number of hospitalizations and emergency visits, we analysed these rates for children under age five, from 2009 to 2014. Children under age five were chosen specifically, because illnesses in this age group can affect the development of children later in life. We also derived annual hospitalization rates of pneumonia, asthma, influenza, upper respiratory disease and gastroenteritis (ICD10 A08-A09) for children under five.”

The findings of this were presented from line 6 to line 23 page 8.

“Trends in children under five

Overall, rates of emergency visits and hospital admissions ….. , For instance, infant admission rates due to pneumonia increased from 19.2 per 1000 in 2009 to 32.4 per 1000 in 2014”

Reference

Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014
Nhung T T Nguyen, Tran Minh Dien, Christian Schindler, Nguyen T B Lien, Nicole Probst-Hensch, Vu T H Lan, Nino Künzli and Laura Perez

BMJ Open 2017 7:
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