Author's response to reviews

Title: Pneumonia and poverty: a prospective population-based study among children in Brazil

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Version: 3 Date: 23 May 2011

Author's response to reviews: see over
Dear Editor

Please find below the point-by-point response to both reviewers.

Sincerely,

Ana Lucia Andrade, M.D.
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Reviewer's report

Title: Pneumonia and poverty: a prospective population-based study among children in Brazil

Version: 2 Date: 29 March 2011

Reviewer: Robert Hall

Reviewer's report:

Review of Thörn, Minamisava et al Pneumonia and poverty

This study provides some useful information on an important topic—the socioeconomic gradient of infectious diseases. The research question is reasonably well defined as an investigation using generalized linear modeling and spatial cluster analysis to determine associations with socioeconomic variables available at census tract level and geographical clustering which can be interpreted using census data and local knowledge. The rationale for the study is clearly presented and reasonable. The methods are well described. The use of the WHO CXR+Pn definition of pneumonia is clear and makes this study comparable with other studies.

1 - It would be reasonable to suspect that many children in the present study had received antibiotics during the course of their illness and this would reduce the sensitivity of a culture-based case definition further.

Reply:
According to the LEAP database 26% of the enrolled children referred use of antibiotic in the previous 7 days. However, blood culture was performed using an automated blood culture system (PedPlus Bactec) which increases the probability of recovering bacterial from patients receiving antibiotics.

The study population is well described and the flowchart of recruitment clearly describes the recruitment process. Eligibility and recruitment processes appear sound.

2 - The authors assert that all clinical services in the geographical area participated, and this should reduce bias. However, it is likely that children from poorer families would be less likely to have a chest X-ray, which may lead to underestimation of the effect of low socioeconomic status on the incidence of pneumonia. Chest X-rays were read by a single author.

Reply:
We have already replied to reviewer2 on this matter:
“The public health care is provided by Brazil’s Unified Health System and covers around 70% of the population in Goiânia. As a rule of the public health system in Goiânia the patient needs to pass through a primary health center before searching for a hospital. In major of cases, the problem is solved at the health center and it reduces lines and waiting time at the hospitals, opening space for those really severe cases. All primary health care facilities have chest X-ray machine. Four out of the 13 primary health care services participated in the present study are located in the Northeast region (see map, figure 1) and 100% of that area is covered by the public family health program”.
Please see page 15.

3 - No sample size calculations were performed.

Reply:
The study had no hypothesis as it was a surveillance study and conducting two-year-surveillance provided sufficient statistical power to detect the burden of pneumonia with narrow 95% confidence interval.

Data analysis was by generalized linear modelling and spatial cluster analysis using a scan statistical procedure. For the modelling analysis it is reasonable to use a negative
binomial model for overdispersed data like these. It is reasonable to take steps to reduce the effects of multicollinearity. The authors conducted univariate analyses on each variable and built a multivariate analysis from the predictors that were significant. There was a nearly three fold increase in incidence of pneumonia from the lowest census tracts with the lowest socioeconomic index to those with the highest. The authors constructed their own index of socioeconomic status from variables available from the census. This index appears reasonable. It is an ecological index so there is loss of sensitivity and specificity, but this is a commonly adopted method.

4 - The clustering analysis was done using a scan statistic, probably with SaTScan software. It is a very conventional analysis, and the steps taken appear reasonable. A cluster is detected, in areas where one might expect higher incidences based on the modelling results. These results are in line with findings of other studies.

Reply:
Yes, we used the SaTScan software to perform spatial analysis of clusters. We included this information in the Methods section, on page 11.

5 - The authors conclude that their results define areas where immunization should be a priority, but it seems hard not to make immunization a priority for all children. The discussion of the impact of pneumococcal vaccination must be speculative, since no data on immunization are presented.

Reply:
You are right. As we responded to the reviewer 2, the text is misleading since immunization should be a priority for all children as a whole, regardless of the SES, and obviously we can’t recommend target approach under universal vaccination. By defining clusters of pneumonia in selected areas the idea is that these areas should be targeted for high vaccination coverage, as stated on page 19.
Reviewer's report
Title: Pneumonia and poverty: a prospective population-based study among children in Brazil
Version: 2 Date: 13 April 2011
Reviewer: Daniel Feikin
Reviewer's report:

Abstract

• Last sentence of results says high income household associated with pneumonia which seems contrary to main geospatial association with poorer census tracts.

  Reply:
  You are right. It was a typing mistake. The correct is “Lower income” (page 2)

• Conclusion. Should change phrasing from “should be kept at high vaccination coverage” to should be targeted for high vaccination coverage as you have not stated in abstract that they already have high coverage.

  Reply:
  Thanks. Done as advised (page 3).

Background

• First paragraph. Too much detail on pneumococcus. That is not the focus of the paper. should lead with association of pneumonia as a syndrome and poverty as a risk factor. You only introduce this idea in 2nd paragraph in sentence starting “Several studies have investigated....” Bring this up into first paragraph.

  Reply:
  Agree with the reviewer. The text was revised and one paragraph was inserted to mention studies on risk factors for pneumonia including poverty (page 4).

• Second paragraph. Too much on development of CXR guidelines by WHO. That is not the focus of the paper.

  Reply:
  This section has been shortened and revised (pages 4-5).

Methods

• Major. First paragraph. Please clarify the discrepancy between 70% persons use public health system but 80% pneumonia seen in private hospitals.

  Reply:
  You are correct. Those who are not familiarized with the Brazilians’s Health Care System may not understand how we can have 70% persons using the public health system and 80% of pneumonia cases admitted in private hospitals. The text was revised to clarify this point. See pages 5 and 6, in “Study Area and Population”.

Do you really think you capture all children with pneumonia in the catchment population in the facilities under surveillance – you state on page 6 “The investigation was conducted at 100% of health services that provide urgent pediatric care in Goiania...”. You must convince reader that wealthier children with pneumonia were not being treated in facilities outside your surveillance area or that were not part of your surveillance system.
Reply:
The investigation really covered 100% of the pediatric emergency services of the city. In fact, a probability exists that we missed a small number of children with high SES who sought attendance in private clinics and not in emergency rooms of hospitals/health centers. I mean children who didn’t seek care in the emergency services so, parents paid to a pediatrician for medical attention. This issue was addressed in the Discussion (page 15) as a potential limitation of the study.

• Major. Page 6. The enrollment criteria are not clear. Was it clinician’s judgment? How was suspicion of pneumonia or invasive disease defined? Symptoms, signs, subjective clinical impression?

Reply:

• Page 6. Not important that blood cultures were done before CXR but more so before antibiotics given. What was timing of culture with antibiotic administration?

Reply:
We added this information on page 7.

• Major. Page 6. In paragraph describing LEAP surveillance, the locations of health facilities involved need to be described. A map would be useful. Did you control for distance to facility in the analysis?

Reply:
A map was added (Figure 1) to display the location of the health facilities involved in the LEAP surveillance. In pages 6-7 we also described the rationale used by the Goiania government to decide on the health facilities location. The government took into account the population density and transportation access to the health services, so an operational plan for improving health services access was developed to support the choice of the geographical location of the health facilities in Goiania. The ultimate purpose was to provide universal and equal access to health services on a decentralized basis. Thus, we did not control for distance to facility in the analysis.

• Major. Page 7. The primary and secondary outcomes imply some children with consolidated CXR pneumonia were not admitted. This seems unusual to treat these children as outpatients since they likely have bacterial pneumonia, yet almost half were treated as outpatients. Describe how decision to admit or not was made? What were criteria used? Was it strictly clinical? Or were there other factors involved, like whether the family could afford and manage outpatient treatment. Is outpatient pneumonia treatment a common practice?

Reply:
The WHO has proposed evidence-based recommendations for the empirical treatment of non-severe pneumonia among children managed by first-level health providers. (WHO, UNICEF: Global Action Plan for the Prevention and Control of Pneumonia in children aged under 5 years. Wkly Epidemiol Rec 2009 and Grant et al.: Invasive pneumococcal disease in Oxford, 1985-2001: a retrospective case series. Arch Dis Child 2003). The majority of pneumonia cases in this study were non-bacteremic pneumonia, as we detected only 62 S. pneumoniae isolates in sterile fluids. Several cases did not reach the criteria for hospitalization as they were non-severe pneumonia even though they presented alveolar consolidation. According to WHO only children with severe pneumonia (presence of chest indrawing, cyanosis, unable to drink or
breastfeed, lethargy or unconsciousness) should be admitted to hospitalization to receive injectable antibiotic. The decision to admit to hospitalization based upon the clinicians’s decision. Antimicrobials for outpatient treatment are free of charge in all 33 emergency health services. In page 7, last paragraph we added a sentence to explain the hospitalization criteria for childhood pneumonia.

• Page 8. Please explain what is meant by “earning more than 20 minimum wages monthly”
  Reply:
  In Brazil, the minimum wage is the lowest amount of salary that employers can legally pay employees for time and efforts spent in producing goods and services. During the study period the mean of the minimum wage corresponded to U$ 312.50 per month. This information is now mentioned in page 9.

• Page 8. Why was 15 years of schooling chosen? What does this mean in Brazilian educational system?
  Reply:
  In Brazil, elementary school is mandatory and lasts for 8 years; people with 12 years of schooling attended at least one year of college. So, we assumed >15 years of schooling as the cut-off to have finished the college. This explanation was provided in page 9.

• Page 8. Give the range of possible SES scores using the system described? Not sure how many “points” can get for each of the two variables.
  Reply:
  Both variables used to build up the SES scores ranged from 1 to 63 points (we added this information in page 10).

• Page 9. Not clear why of the 7 SES variables you looked at you chose only those 2 variables to create the score. Explain choice.
  Reply:
  This is an interesting point you have raised. The text was revised to better describe the purpose of using both, the 7 and 2 SES variables (page 9).

• Page 9. Data analysis. State unit of analysis. Was it district?
  Reply:
  The spatial unit of analysis was the urban districts. Goiania has a total of 63 urban districts (page 10).

• Page 9. Not sure what distribution was positively skewed? Skewed by age? By location?
  Reply:
  The distribution of pneumonia cases was positively skewed by location, districts (page 10).

• Major. Page 10. Please describe how the clusters defined by geospatial software overlapped with district? It is not clear how you used the defined clusters to then come up with a RR by district. I would assume the clusters defined by the program are not same as districts as defined geopolitically.
  Reply:
  In fact, the RR by district was not explored in the spatial analysis. On page 11, we presented the explanation on how the spatial clusters were defined: “The scan statistic used aggregated total number of pneumonia patients and the population at risk in each district and created a large number of elliptical areas (windows) over the study region, each one considered a possible cluster candidate. For each window, the likelihood is calculated based on the observed and expected number of cases inside and outside the area. The area with the
maximum likelihood is defined as the most likely cluster. A district is considered to be part of that cluster if its centroid is included on that window. Monte Carlos simulations using 999 replications was used to test for statistical significance. Both most likely cluster and the non-overlapping secondary cluster were reported along with their corresponding relative risks and p values.”


Reply:
We found no difference on age of children by hospital. The proportion of hospitalized and nonhospitalized patients did not differ neither if taking into account education and income of head of household. Non-hospitalized cases spread more within the municipality area compared with hospitalized children (see page 12).

• Page 12. It seems strange that PCV was distributed also with SES tracts since only available in private market? Explain in discussion.

Reply:
During the period the study was conducted, pneumococcal conjugate vaccine was administered free of charge by the Brazilian Ministry of Health for children who were at higher risk for pneumococcal diseases. Conditions associated to the increased risk of pneumococcal infection are those mentioned in page 6. Therefore, this is the reason children who received the PCV were randomly distributed within the municipality. We rephrased the sentence to clarify this point. Please see page 16.

• Page 12. It is more conventional to give 95% CI around RR, rather than p value.

Reply:
We agree that presenting RR and confidence intervals are common practice in epidemiology; nevertheless, results on spatial epidemiologic analysis are only presented as mapped RR with no attempt to report the uncertainty of the risk estimates. (Beale et al.: Methodologic issues and approaches to spatial epidemiology. Environ Health Perspect 2008). We sent an email to Dr. Martin Kulldorff on this subject and he said: “In a standard epidemiological study, I agree with the reviewer that it is important to calculate confidence intervals and not only p-values, but unfortunately, it is not possible to calculate confidence intervals around the relative risk estimates obtained from spatial scan statistics. You are welcome to quote me on that in your response to the journal”.

• Page 12. I think you mean second cluster rather than secondary cluster. Correct?

Reply:
It is standard to call secondary clusters all clusters that are not the most likely ones. In our study we searched for non overlapping secondary clusters.

• Page 12. Please clarify the meaning of the following sentence “In this way the relative risk for the spatial scan statistics was conservative but strong enough to show the high risk area in northwest region.” The analysis of suspected pneumonia is not clearly described in methods? Is this analysis based on clinical diagnosis rather than CXR?

Reply:
The point we are trying to make is related to bias on geographical distribution of chest radiograph missing pneumonia cases. The pneumonia cases without chest radiograph were not included in the spatial analysis. The majority of these missing cases were located in the northwest region, as the most likely cluster. In this way we meant the spatial scan statistics was conservative, because we found a cluster of CXR+Pn in an area where we “lost” cases. We added this information on page 18.
Discussion

- 1st paragraph. Not clear where the 80% higher comes from. If that is the bottom line finding it is not clear in the results.

Reply:
The 80% comes from RR=1.78, mentioned in the second line, 4th paragraph, page 13, of the Results section.

- Major. 2nd paragraph. “Living conditions and hygiene, rather than access to services, likely played an important role in higher risk of pneumonia in low income areas of Goiania.” This study does not support this statement. It is unclear if poor families seek care later than wealthy families when ARI has progressed to pneumonia without early antibiotic treatment. Besides hospitals what other health care facilities might children be taken to receive treatment and would pre-hospital treatment be less common for the poor? Are antibiotics available at pharmacies without prescription? There could be health seeking component to this difference. Health seeking is more than just distance to facility.

Reply:
The public health care is provided by Brazil’s Unified Health System and covers around 70% of the population in Goiânia. As a rule of the public health system in Goiânia, the patient needs to pass through a primary health center before search for a hospital. In major of cases, the problem is solved at the health center and it reduces lines and waiting time at the hospitals, opening space for those really severe cases. All primary health care facilities have chest X-ray machine.

Concerning availability of antibiotic without prescription – Yes, to the date of this study it was possible to buy antibiotics at pharmacies without prescription. By using primary data obtained by LEAP study we observed a lower proportion of self-medication with antibiotic inside the most likely cluster compared to areas outside the CXR+Pn clusters (data not shown).

It is not possible to ascertain if poor families seek care later than wealthy families when acute respiratory infection has progressed to pneumonia without early antibiotic treatment. However, evidence exists that the number of people seeking primary health care have markedly increased in recent years and people with serious health disorders are able to seek health care and receive treatment, irrespective of their socioeconomic class (Victora et al: Health conditions and health-policy innovations in Brazil: the way forward. Lancet 2011, Doi:10.1016/S0140-6736(11)60055-X, in press).

These issues were discussed on page 15.

The discussion of explanations for higher incidence in the poor needs to be expanded to include not just difference in health care seeking and access to antibiotics, but other factors such as increased exposure to pathogens in crowded living conditions (e.g. increase viral transmission, increased risk of bacterial pneumonia), differences in underlying illnesses that predispose to pneumonia (e.g. malnutrition), and differences in vaccination.

Reply:
We included these suggestions on page 14 as:
“It is well recognized that increased exposure to viral and bacterial agents in crowded conditions, such as institutionalized environmental, may contribute to increased risk of pneumonia in children (Andrade et al 2004. IJE), besides underlying illnesses as malnutrition (Fenn et al 2005)”.
• Major. 2nd paragraph. Page 13. Is it possible that illegal settlers don’t seek care early because of their illegal residence status? Would they not qualify for public care because they officially are not residents of the area?
  
  **Reply:**
  Although the northwest region was invaded by illegal settlers in the 1980s, since 1990’s the government provided housing for all the residents. Even though, the northwest area still concentrates poor families. Four out of the 13 primary health care services participated in the present study are located in the Northeast region (see map, figure 1) and 100% of that area is covered by the public family health program. We dealt with this issue on page 15.

• Page 14 top. I don’t follow the math. If only half of pneumonias are outpatient, shouldn’t the incidence have doubled in the current study from the previous one on hospitalized patients – it was 4.3 times higher. Please explain.
  
  **Reply:**
  Studies shows that the pneumonia incidence increases > 2-fold when children are enrolled at outpatient level than among patients enrolled at the hospital admission (Lagos et al 2006). The inclusion criteria differed between surveillances, the previous one and the present study. The first investigation included hospitalized children with clinical suspicious of pneumonia. The second surveillance enrolled children who presented to both, outpatients or inpatients with flu-like symptoms or clinical suspicious of pneumonia or fever > 39oC. Therefore, the present surveillance used a more sensitive algorithm to capture pneumonia cases, while the previous surveillance captured only inpatient cases, considered more severe cases. We added these explanations on page 16.

• Page 15. “One limitation of this study is the possibility of ecological fallacy since area-based socioeconomic data may not represent the individual-level socioeconomic status.” This is not an example of ecological fallacy, although it could still be a limitation. The ecologic fallacy would be that the association between poor areas and pneumonia is true, but confounded by another factor that actually is leading to pneumonia increase, such as different elevation or rainfall.
  
  **Reply:**
  This is a good point. Differently of what occurs in other regions, we don’t have striking temperature variations along the year or even geographic elevations in the municipality of Goiania. We took advantage of your comment to improve the text on pages 17-18.

• Major. Page 16. Should discuss how PCV should even the differential between incidence in poor and wealthy in Brazil. Cite studies from US that showed IPD rates between white and black children became more similar after PCV introduction. You mention that the study highlights areas that should be priority areas for vaccination. But isn’t vaccination a national program, without targeted areas. Would not suggest a targeted approach if universal vaccination. Rather could stress that extra efforts should be made to get poor children in for vaccination. Are there differences in vaccination for other EPI vaccines by economic status of districts?
  
  **Reply:**
  You are correct. The text is misleading. In Brazil there are no differences in delivering vaccination regardless of the SES, and obviously we can’t recommend target approach if universal vaccination. We text was revised accordingly (pages 16 and 19).

• Discussion should mention that the case definition is more for bacterial than viral pneumonia. how might that affect results?
  
  **Reply:**
Actually, in the 2\textsuperscript{nd}-year surveillance the eligibility criteria were expanded to also include patients with flu-like symptoms hence viral pneumonia. It is possible that we missed cases that would have progress from “viral pneumonia pattern” to alveolar consolidation. The radiological definition of pneumonia by WHO we have used herein take into account cases that present a radiograph compatible with pneumonia of bacterial origin. (page 18)

- Major. Discuss potential bias and its direction of one area NW Goiania accounting for disproportional amount of missed CXRs, since this is same area with highest incidence.
  
  \textbf{Reply:}
  Most of the missed cases (children without available chest X-ray) resided in the NW region. As the high incidence of radiologically pneumonia was also in NW region we could assume that potential bias, if present was towards the null (included on pages 17-18). If we had more pneumonia cases in that area the RR would be higher than the one that we have found – in this way the reported RR is underestimated.

- Major. Might the referral for admission be confounded by socioeconomic status. Among those not referred for admission, were they of higher SES? Might clinicians have felt that these were more reliable and educated families who could better manage pneumonia treatment at home? Is this a bias?
  
  \textbf{Reply:}
  Interesting point indeed. We deal with this potential bias on page 18. “Someone could argue a possibility of referral for admission is confounded by socioeconomic status, as a potential source of selection bias. Clinicians might have felt that more reliable and educated families could better manage pneumonia treatment at home. If so, we could expect that a selection bias on hospitalization, however without affecting the study outcome”