TITLE

Prevalence of wheezing disorders in children in areas covered and not covered by the Family Health Strategy in Jaboatão dos Guararapes: Cross-sectional study.

Prevalência de doença respiratória com sibilos em crianças em áreas cobertas e não cobertas pela Estratégia de Saúde da Família em Jaboatão dos Guararapes: estudo de corte transversal.

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INTRODUCTION

Early childhood wheezing disorder includes many different phenotypes and aetiologies, such as asthma and viral respiratory infection. Brazil has a high prevalence of asthma in children and wheezing disorders in infants (Mallol 2013; Mallol 2016) and there is evidence that most cases of asthma in Brazil are not attributed to atopy (Cunha 2010a). There is also evidence suggesting that modifiable environmental conditions play an important role in the causation of asthma (Mallol 2013), such as tobacco smoke for wheezing disorders in general, and it is thus possible that public health interventions may change the occurrence of disease even when these interventions are not directed to control of these diseases. Most of the municipalities in Brazil are covered by the Family Health Strategy (**FHS**), in which each FHS unit comprises a primary care centre and a health team with municipal community health workers (in Portuguese: *agente comunitario de saude,* **ACS**). Each ACS is responsible for delivering health interventions at local basis, such as vaccination and health education and to schedule medical visits in the primary care units (description of FHS can be found in (Johnson 2013)). The activities of the ACS are unlikely to change outdoor environmental factors, but can potentially change indoor environment (e.g. promotion of smoking cessation).

Here we describe a cross-sectional study with children between 2 months to 4 years of age living in a poor metropolitan area of Brazil. The two primary objectives were: 1) to estimate the prevalence of lower respiratory disease (**LRD**) especially those with wheezing (in this case hitherto defined as having wheezing disorders, **WD**) and 2) to compare the prevalence of LRD between children who were living in areas covered by the FHS and children not living in areas covered by the FHS. We have also assessed 3) if the prevalence of potential risk factors for LRD differed between the two areas and 4) the association between these potential risk factors and WD. Given the importance of wheezing disorders we also discussed the possibility of control in this age group in the context of the FHS. This manuscript followed The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (von Elm 2014).

METHODOLOGY

Study site.

This survey was conducted in the municipality of Jaboatão dos Guararapes (**JG**), North-east Brazil. It had 644,620 inhabitants in 2010, an average per capita income of R$593.90 (approximately US 330.0) while in Brazil was R$793.87 and a GINI index estimated as 0.58 in 2010 (Atlas do Desenvolvimento Humano do Brasil 2013). The study population was from two contiguous urban areas located at the main residential and commercial centre of JG: 1) **FHS areas** covered by 8 FHS units with 52 ACS in total, and 2) areas not covered by the FHS (**non-FHS areas**) but covered by 6 municipal health workers responsible for dengue control (ACD). Activities of the ACD were restricted to dengue control, for example, to identify and destroy breeding sites.

The target population.

It is the population from which the studied sample was drawn. It comprised all children between 2 months to 4 years of age residing in these selected FHS and non-FHS areas (children aged 5 years or older were excluded). This age group was selected because it was reported as having the highest risk of LRD with wheezing in a survey carried out in another municipality in North-east Brazil (Cunha 2010b). Based on the list provided by the FHS units, there were approximately 2,100 children aged 0-4 years living in FHS areas. There was no such list in the non-FHS areas and the estimated target population was roughly estimated based on: 1) the number of residences listed by the ACDs (n = 4,800), multiplied by the 2) average number of persons by residence (3.5)[1] and by the 3) proportion of the total population in the municipality aged 0-4 years in 2010 (0.072)[2]. In total, the estimate for the non-FHS areas was roughly 4,800 x 3.5 x 0.072 ~ 1.200 children.

Sampling.

For areas covered by FHS, we first selected 25 ACSs randomly (among the original 52 ACS), In non-FHS areas, we carried out home to home visits in predominately residential areas covered by 6 selected ACDs.

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[1] Pesquisa Nacional por Amostra de Domicílios, IBGE, 2009, para a Região Nordeste, item 6 Domicílios, tabela 6.2, http://www.ibge.gov.br/home/estatistica/populacao/trabalhoerendimento/pnad2009/default.shtm

[2] In 2010 census, the total population for the municipality was 644,620 and for those aged 0-4 years was 46,500, thus the proportion is 46,500 ÷ 644,620 = 0.072

Sample size.

This study had several objectives. The sample size was calculated specifically to detect the difference in the prevalence of LRD between FHS and non-FHS areas. At the time of writing the protocol, we consulted several estimates for prevalence of LRD reported in published papers (**Table 1** below) and we decided arbitrarily to assume a prevalence of 20% for LRD in the total study population.

Table 1. Estimates of lower respiratory disease in different published studies

Reference	Study site	Study design[1]	Age	Definition of outcome	Prevalence (%)
Lye (1994)	Malaysia	CS	≤ 7 years	Symptoms in the last 2 weeks Mild: cough, coryza, sore throat Moderate: fast breathing	Mild = 28.0% Moderate = 0.4%
Prietsch (2008)	Brazil	CS	< 5 years	Symptoms in the last 1 week Cough, shortness of breath (wheezing among those < 2 years of age)	23.9%
Luby (2008)	Bangladesh	CS	< 5 years	Symptoms in the last 1 week Cough, coryza, shortness of breath	25.0%
St Sauver (1998)	USA	CS	≤ 12 years	Symptoms in the last 5 days Cough, coryza, sore throat, ear pain	11% to 18%
Victora (1990)	Brazil	CO	12-24 months	Children hospitalised due to pneumonia in 1985	3.3%
Cunha (2010b)[2]	Brazil	CS	4 years	Symptoms in the last 12 months At least one of the following: diagnosis of asthma ever, wheezing with exercise, 4 or more episodes of wheezing, waking up at night because of wheezing	37.4%
Martinez (1995)	USA	CO	3 years	Questionnaire: whether the child's "chest had ever sounded wheezy or whistling apart from colds"	Transient wheezing: 19.9% Persistent wheezing: 13.7% Total: 33.6%
Muino (2008)	Brazil	CO	4 years	Symptoms in the last 12 months Presence of wheezing	Transient wheezing: 43.9% Persistent wheezing: 6.4% Total: 50.3%

Notes: [1] CO = cohort, CS = cross sectional; [2] this study was published after the protocol but the results were known by the main author of this survey

In order to calculate the sample size aimed to compare two proportions, we needed to define whether or not the groups would have equal size, the expected prevalence of disease in each group, the study power and significance level (Whitley 2002). We then assumed the following assumptions:

1. Sample with equal number of children in 2 areas (FHS and non-FHS areas);
2. prevalence in areas with FHS of 15%;
3. prevalence in non-FHS of 25%;
4. study power of 90%;
5. alpha error of 5%.

The estimated sample size was 373 children in each group (Table A.3 in (Fleiss 1973)), a minimum of 746 children in total. Due to the possibility of clustering effect and low response rate among children who were initially sampled (unit missing data)[3], this size was arbitrarily increased 50% and therefore our target was to select a sample of 1,120 (~746 x 1.5). Response rate is defined here as "the number of participants divided by the sum of the numbers of participants, nonparticipants (including refusals and non-contacts), and persons of presumed but unconfirmed eligibility" (Morton 2006). Low response rate could affect the sample size if, for example, it was initially sampled 800 children but only 600 could be found, what is bellow the 746. Clustering effect happens as: "Individuals may interact within the cluster, leading to similarities between individuals for some health related outcomes" (Ukoumunne 1999). When this happens, it is not possible to consider individuals within the same cluster as independent to each other and thus it is said that clustering effect is present. The presence of clustering effect increases the standard errors of the estimates and consequently increases the sample size required for the study.

Field work.

The survey was conducted in 2011 (from January to July) with home visits by interviewers (health students) trained in a pilot field work. In FHS areas, a list with addresses of all children aged 2 months to 4 years was available provided by the community health workers (ACS). In these areas, children were only excluded from the study after at least 3 attempts to interview the mother or responsible.

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[3] **Unit missing data** (or **unit** nonresponse) means "... a subset of sampled individuals [that] do not complete the questionnaire", for example individuals who refused to participate after having been selected. In contrast with **item missing data** (or **item** nonresponse) which means "missing values on particular items in the questionnaire", for example, when sampled individuals refuse to respond on their salaries, these individuals have questionnaires but the questionnaires are incomplete (Little 2002).

There was no similar list in non-FHS areas and so each household was visited just once. In both areas, the guardians, mainly the child mothers, were interviewed after the completion of an informed consent letter and their consent were given. All eligible children contacted were included in the sample, even when a mother had more than one child. Several FHS and non-FHS areas were excluded during the field work due mainly to high health risk for the field workers, for example: reports of street gangs operating in the areas, flooding, large amount of raw sewage in the street, and difficult access (mainly steep hills). In FHS areas, exclusions were replaced by other ACS and their respective catchment areas randomly selected. In non-FHS areas, there was no replacement because we worked with all potential residential areas.

Questionnaire and definition of outcome

The questionnaire had 1) multiple choices and 2) open questions on respiratory symptoms, use of medications, hospitalisations and primary care consultations, and was adapted from previous studies based mainly on the ISAAC questionnaire (Sole 1998; Barreto 2006; Dela Bianca 2009). The precise diagnosis of wheezing disorder in this age group, as asthma, is subject of uncertainties. Because of that, in the analysis we opted to categorise children in four groups, which corresponded to the dependent variable with 4 categories, three categories representing disease status and 1 reference category (see terms and **Figure 1** below).

Frequent wheezer (FW), if child had several episodes of wheezing defined by the criteria:

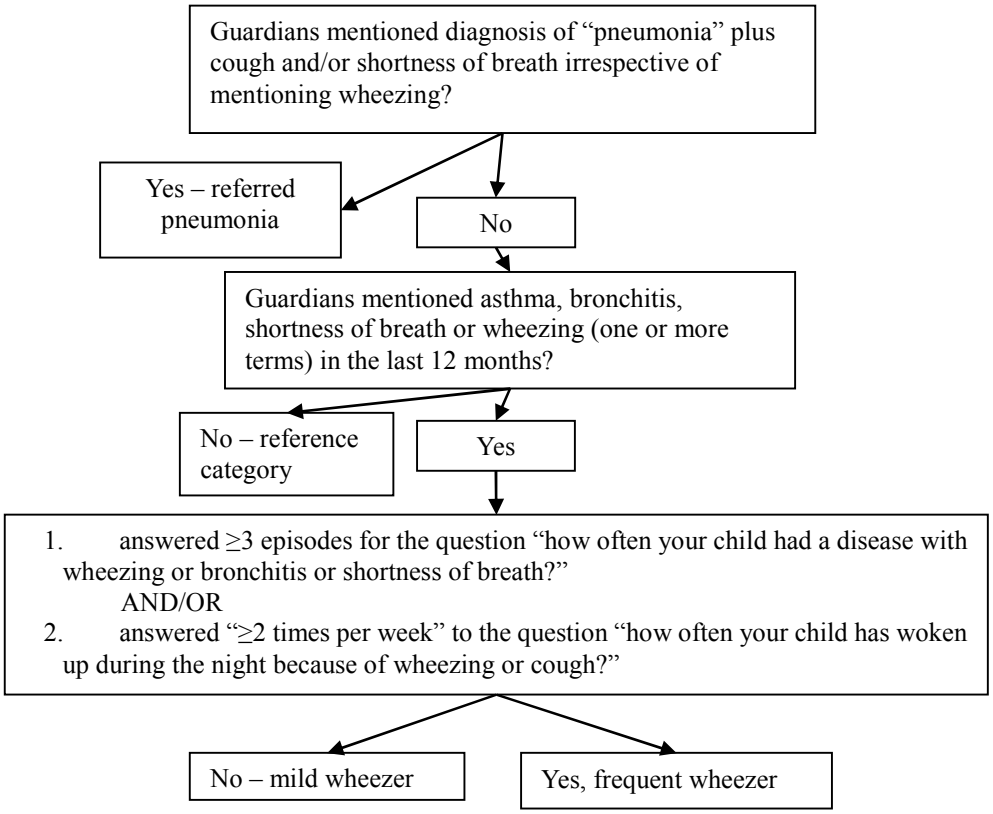
1) the guardians mentioned asthma, or bronchitis, or shortness of breath or wheezing (one or more terms) in the last 12 months; and
2) any of the two:
    a. the guardians answered ≥3 episodes for the question “how often your child had a disease with wheezing or bronchitis or shortness of breath?”;
    b. answered “≥2 times per week” to the question “how often your child has woken up during the night because of wheezing or cough?”.

Mild wheezer (MW), if child had criterion 1) above, but not criterion 2).

Referred pneumonia (RP), if the guardians mentioned 1) diagnosis of "pneumonia" **and** 2) cough and/or shortness of breath irrespective of mentioning wheezing as the two previous groups. This category **RP** cannot be taken as an accurate diagnosis of pneumonia, but more appropriately as suspected cases of pneumonia as well as more severe cases of wheezing disorders.

Reference category, if child had no respiratory symptoms or unspecific symptoms (not related to LRD, e.g., sneezing and blocked nose).

Figure 1. Algorithm to define outcomes



We decided not to use and follow strictly the questionnaires such as the International Study on Wheezing in Infants (**EISL**) (Chong Neto 2009) or other. This was mainly because: 1) our study was to apply a questionnaire during home visits to collect data on disease how it is observed in the community instead of patients attending health centres (such as EISL (Chong Neto 2007; Chong Neto 2009)); 2) use of medications is included in others questionnaires, but in our pilot study questions citing medications had low response rate or not always consistent with what was retrieved in the medication packages; 3) it is well known that the clinical spectrum of a disease can vary in different

study settings and prevalence of disease (Knottnerus 2003). Therefore, we were worried specially about spectrum bias (Knottnerus 2002) and misclassification of the disease status. We then decided to elaborate the final version of our questionnaire with the following order of questions: 1) symptoms similar or the same questions used in previous questionnaires (ISAAC and EISL); 2) not to question whether a doctor gave the diagnosis of asthma (such as in (Chong Neto 2007; Chong Neto 2009)) but asking the name of the disease given by the doctor or other health professional to avoid inducing answer; 3) whether or not had used medication; 4) name of the medications (but the questions did not mention brand or generic name); 5) question for the medical prescription or medication package to compare with the name given by the interviewee; 6) whether or not child had been in any health service for respiratory disease and used nebulisation. The questionnaire was revised for authors with clinical experience in paediatric respiratory disease (MCAB and PAMC) and in this way, we try to guarantee the content validity.

Predictor variables for LRD

The potential risk factors for LRD were classified into 1) whether or not were considered potentially modifiable by the activities of ACS, 2) related to outdoor or indoor environment, 3) characteristics of children or mother and families. The list of risk factors is provided in **Table 2** below.

Table 2: potential risk factors for respiratory disease used in the survey

Group of variables	Whether considered as potentially modifiable by the family health system (FHS)	
	Non-modifiable	Potentially modifiable
Outdoor environmental conditions	Regularity of garbage collection, presence of open sewage, garbage in the streets, stray animals, whether there is flood in the street when raining, presence of pavement in the street	-
Indoor environmental conditions	Piped water in the house, number of people living in the house, number of rooms used to sleep, type of housing (room, shanty, house, apartment building), type of floor	Presence of mould and pets in the house (dog, cat and birds)
Individual characteristics of children	Age of children, sex, whether have been in nursery	Lack/insufficient of total and exclusive breastfeeding, birth weight, vaccination, medication and whether have been taken to health services for respiratory disease
Individual characteristics of mothers and families	Mother: age, occupation and paid job, skin colour, whether had someone who helps her to look after the study child, lived with partner, had another child who died previously the survey, social support and social network**,** schooling; Mother or other family members living with the mother: received social benefit, respiratory disease, history of asthma, family income.	Maternal smoking or other family member, use of alcoholic drink

Total duration of breastfeeding was defined as any breastfeeding, and **duration of exclusive**

breastfeeding as the age that other milk, water, tea or solid food was introduced. The questionnaire had six questions on **social support** and five on **social network** used in previous work (Chor 2001), each question having a score from 1 to 5. In these items we use the questionnaire presented in (Chor 2001) but we decided not to use all questions, because in our pilot study some questions were not completely understood by the interviewees[4]. **Presence of mould** was determined mostly by visual inspection conducted by the interviewer and/or referred by the interviewee (the questionnaire had a description on how mould patches would look like to facilitate the correct identification). **Vaccination** was ascertained through vaccination cards.

Analysis

Variables in the analysis. For continuous predict variables, we created categories decided a priori in the analysis plan based on biologic information and literature (to avoid data dredging due to "data torture" (Marshall 1990; Mills 1993)), or based on the results of univariable analysis as equally spaced boundaries (Greenland 1995). Variables on social network and social support were initially assessed for internal consistency with Cronbach's alpha (Bland 1997), and then variable with the sum of the scores was created and categorised based on visual inspection. We performed two types of analysis to assess predictor variables, as summarised in **Table 3** below. The analyses followed the steps from bivariable analysis to multivariable as described in the **table 4** and the description below.

[4] We used to social network all 5 questions previously described (Chor 2001) but we added the question "If there was a problem in our community, neighbourhood or street, for example, problem about sewage system or garbage collection, do you think that your neighbours would be united to find a solution?". The consistency was analysed with and this question. To social support we used the 6 questions D6, D8, D9, D11, D14 and D19 described in (Chor 2001).

Table 3: Analyses

	Analysis 1 Distribution of risk factors for LRD	Analysis 2 Risk factors associated with LRD
Objective	To assess the distribution of potential risk factors comparing FHS and non-FHS areas	To estimate the association between potential risk factors and the three categories representing of LRD (FW, MD and RP)
Outcome/dependent variable	Dichotomous: FHS vs non-FHS areas (reference)	Four categories, reference (no disease) vs frequent wheezer, mild wheezer and referred pneumonia
Exposures/independent variables	Risk factors for LRD	Risk factors for LRD
Analysis unit	Each household and family/mothers	Each child
Cluster	ACS or ACD	Mother
Regression	Logistic, unweighted and weighted	Multinomial, unweighted and weighted
Model building	Non-automatic backward elimination	Non-automatic backward elimination
How to deal with missing data	Complete case analysis and multiple imputation	Complete case analysis and multiple imputation

LRD: lower respiratory disease; FHS and non-FHS: areas covered and not covered by family health system; ACS: community health workers; FW, MD and RP: frequent wheezer, mild wheezer and reported pneumonia.

Table 4: Steps used in the analyses

	Bivariable	Multivariable analysis		
		Complete case analysis	Multiple imputation	
		Unweighted[1]	Unweighted	Weighted
Objective	Selection of independent variables to enter in the multivariable analysis	To assess association between independent variables and the outcome.		
Number of individuals analysed	Varied with the number of individuals without missing data for each independent variable	Fixed but it included only those individuals without missing data for all variables analysed	Fixed and it included all except 4 individuals in the dataset	
Control for confounding	No	Yes	Yes	Yes
Weighted	No	No	No	Yes
Adjustment for clustering	No	Yes[2]	Yes	Yes
Note on study power	Underpowered because smaller number of individuals analysed (not all dataset)		Study power corresponding to the almost all individuals in the dataset	
Assumption on missing data	Missing complete at random (MCAR)		Missing at random (MAR)	
Note on interpretation and generalisation of the results	Assumption that those variables with p value > 0.20 would not have association with the outcome.	Results generalised for the population sampled if it was "missing data complete at random" (**MCAR**) and the composition of the population analysed is similar to target population (**similar sampling probabilities**)	Results generalised for the population sampled if it was "missing data at random" (**MAR**) and the composition of the population analysed is similar to target population (**similar sampling probabilities**)	Results generalised for the population sampled if it was "missing data at random" (**MAR**), but **because of the weights, the results are not necessarily the same for the set of individuals analysed**

Note [1]: Weighted analysis using only children without missing data can result in results that are not representatives of the target population where the sample was drawn (Simpson 2004); [2] CCA analyses were performed twice, with and without adjustment for clustering, but because the p values and 95% C.I. were essentially the same, only unadjusted results are presented.

Bivariable analyses. Variables with a P value ≤ 0.20 in the bivariable analysis entered in the multivariable analyses (Sun 1996; Greenland 2008).

Multiple imputation (MI). Each of the two analyses presented in Table 3 was repeated twice: 1) complete case analysis (CCA, only individuals without missing data for the variables included in the analysis) and 2) with multiple imputations (MI) (Sterne 2009) with or without weights.

On MI. There is no consensual opinion about what is the proportion of missing data that would justify MI (Dziura 2013), as selection bias due to missing data depends also on the mechanism of missing data and the differences between individuals included and excluded in the analyses (Newgard 2007). We decided to perform MI for the reasons below:

(1) The aggregate rate of missing data, for example when several variables are used in multivariable analyses, was ~ 20%, despite the fact that proportion missing data for individual variables was low (between <1% to 4%); also, the proportion in missing data for birth weight, an important predictor for LRD, was high;
(2) The exclusion from an analysis of variables with high proportion of missing data or the exclusion of individuals with missing data in variables used in multivariable analysis, can lead to selection bias (Horton 2007; White 2010a);
(3) Weighted analysis ("sample selection probabilities") using only children without missing data can result in results that are not representatives of the target population where the sample was drawn (Simpson 2004);
(4) Before the main analysis, we performed analysis about missing data. We observed that in the variables with missing data, the observed data (in those individuals without missing data) could be predicted by some other variables in the database; also, whether a variable had missing data could be predicted by other variables in database. This pattern characterises "missing at random pattern (MAR)" in which MI is in general recommended, and it was assumed this pattern in the analyses (White 2010b);
(5) Analysis with individuals without missing data can be biased (van der Heijden 2006; Janssen 2010).

The multiple imputation was conducted following the procedures:

1. Chained equations" (White 2010b; Azur 2011), which is as efficient as the alternative method (Lee 2010);
2. Included the respective outcomes, variables associated with the outcomes, predictors of variables and values with missing data, sampling units (Moons 2006; White 2010b) (Sterne 2009);
3. With 20 imputations (White 2010b);
4. Weights were included in the multiple imputations (Reiter 2006; Heeringa 2010).

Weighting. Weight was the reciprocal of the product of the sample probabilities and response weights (Heeringa 2010).

Modelling. In all analysis, odds ratio was used as association measure as recommended (Reichenheim 2010). Multivariable analyses followed a non-automatic backward elimination based on p values and change-in-estimate approach. All MI analyses were adjusted for clustering and weighted and assuming missing at random with chained equations and 20 imputations. CCA analyses were unweighted and performed twice with and without adjustment for clustering (only unadjusted results are presented).

Goodness-of-fit was assessed with Hosmer-Lemesow test (Hosmer 1997). Results are presented for those variables with a P value ≤ 0.10, and separately for CCA and MI as recommended (Sterne 2009). All the analyses were done in STATA version 12 and for complex surveys and multiple imputations using commands svy and MI. Design effect was estimates using the command "estat effects"[5]. The final analysis was carried out in 2014. Statistical significance was defined as $P < 0.05$.

Ethical approval. This study was approved by the local ethics committee at the Federal University of Pernambuco, Brazil.

[5] "When planning a survey, the sample size must account for potential correlation in the data [clustering effect]. A common approach is to estimate an 'effective' sample size, *n*, with a formula that does not account for correlation, and then to calculate a final sample size by multiply *n* by an estimate of the design effect. The design effect is the ratio of the actual variance of a sample to the variance of a simple random sample of the same number of elements". (Rowe 2002)

Results

In FHS areas, 773 children included in the original list of those aged <5 years were visited but 161 (20.8% of 773) were not included in the study for several reasons: 37 refusals, 54 children not found, 17 guardians not found, 8 the guardians were not eligible to sign the consent letter (minors without the presence of their parents or adult parent of the children), and 29 for other reasons. Additionally, questionnaire was applied in 16 children included in the list but later were identified as having age below 2 months or above 4 years. The remaining 612 children were included in the study. There were no refusals in non-FHS areas and data from all 299 children contacted and interviewed were included. In total, there were 911 children from 763 families.

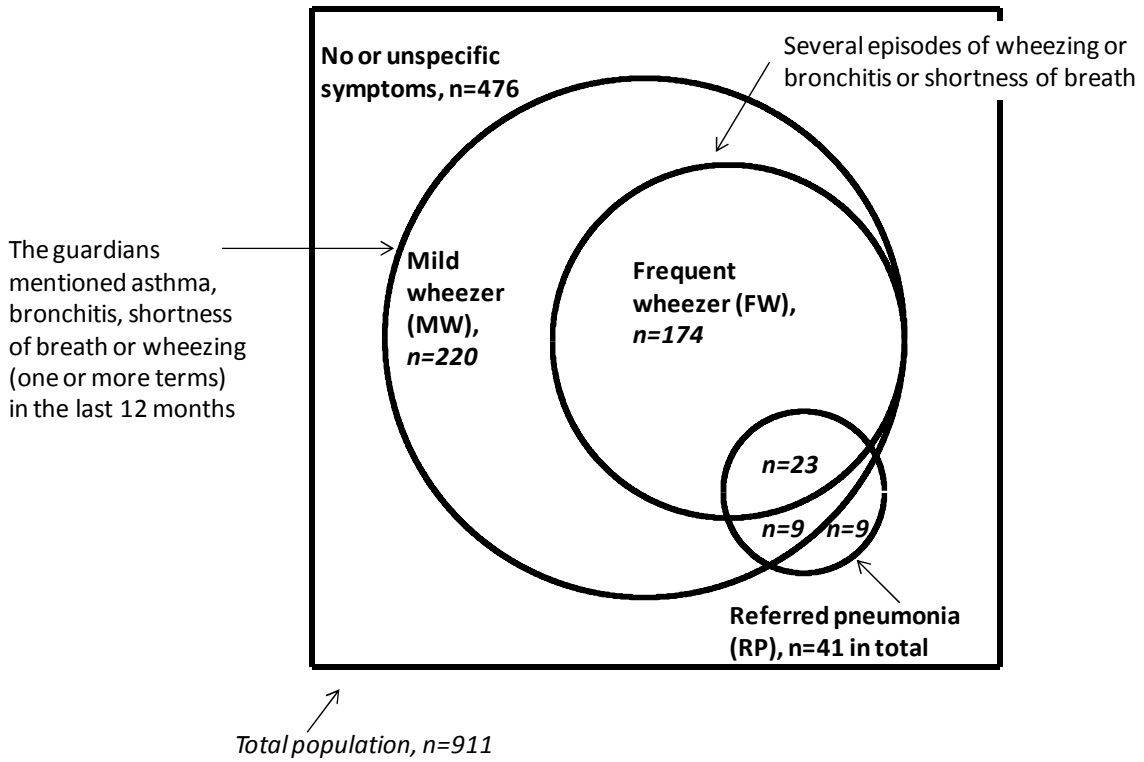
Frequency of respiratory disease and symptoms are presented in **Table 5** and **Figure 2** below. Among 911 children, 220 (24.1%) were classified as mild wheezer, 174 (19.1%) as frequent wheezer (**Table 5**) and 41 (4.5%) had referred pneumonia (these percentages correspond to the unweighted prevalence rates of LRD for FHS and non-FHS areas together). Among these 41 children with referred pneumonia, 9 (22.0%) had also symptoms compatible with mild wheezer, 23 (56.1%) with frequent wheezer and 9 (22.0%) had no wheezing (**Figure 2**).

Table 5: Distribution of 911 children aged 2 months to 4 years according to respiratory disease and symptoms

Disease	N	Cough		Shortness-of-breath		Wheezing		Antibiotic[1]		Hospitalisation	
		n	%	n	%	n	%	n	%	n	%
Reference	476	211	44.3	5[2]	1.1	0	0	16	3.4	7	1.5
Mild wheezer	220	164	74.6	163	74.1	120	54.6	25	11.4	17	7.7
Frequent wheezer	174	152	87.4	145	83.3	110	63.2	20	11.5	28	16.1
Referred pneumonia[3]	41	34	82.9	27	65.9	24	58.5	17	41.5	17	41.5

Note: [1] recognised by the medical prescriptions and/or packages; [2] occurred more than 12 months before; [3] some of them also had wheezing (see figure 2 below)

Figure 2: Veen diagram with the relation between children categorised in 4 four groups



The weighted and unweighted prevalence rates are presented in **Table 6** below. The prevalence was slighter higher in FHS than in non-FHS areas but the difference was not statistically significant. The greater contrast was on RP: 5.5% in FHS areas and 3.1% in non-FHS areas (prevalence ratio = 1.77; 95% C.I.: 0.75-4.20, weighted and adjusted for clustering mothers as cluster).

Table 6: Weighted and unweighted prevalence of respiratory diseases separately for FHS and non-FHS areas.

Disease	Number of children			Prevalence %			
	FHS areas	non-FHS areas	Total	FHS areas		non-FHS areas	
				unweighted	weighted	unweighted	weighted
Reference	309	167	476	50.5	50.3	55.9	60.7
Mild wheezer	152	68	220	24.8	25.4	22.7	21.5
Frequent wheezer	122	52	174	19.9	18.9	17.4	14.8
Referred pneumonia	29	12	41	4.7	5.5	4.0	3.1

FHS and non-FHS: areas covered and not covered by family health system

Design effect. We estimated the design effect given mothers as cluster unit and it varied between 1.00 (for referred pneumonia) and 1.10 (for mild wheezer), **Table 7** below.

Table 7: Estimates of design effect.

Among the same 907 children with weights[1]	Standard error (SE) for proportions (prevalence) of the outcomes		
	Mild wheezer	Frequent wheezer	Referred pneumonia
Without any adjustment for clustering	0.014196	0.0130814	0.0069021
Adjusted for mother as cluster	0.0148617	0.0132607	0.0068636
Design effect **(DEFF)**[2]	1.095986	1.0276008	0.98887509

Notes: [1] 4 children excluded from this analysis; [2] it is calculated as (SE model with adjustment 2 ÷ SE model with adjustment)^2, for example, for mild wheezer it is $(0.0148617 \div 0.0141960)^2 = 1.095986$

Use of medication. Among 151 children with FW (n=122) or RP (n=29) living in FHS areas, in 32 (21.2%) the guardians mentioned have received a medical diagnosis of "asthma", and in 59 (39.1%) the name of bronchodilators or their brand names were recognised (in medical prescriptions and/or mentioned). In contrast, in 64 children living in non-FHS with FW or RP these figures were 7 (10.9%) and 21 (32.8%), respectively.

Service utilisation. For the 151 children with FW or RP in FHS areas, 130 (86.0%) went to primary care services, 112 (74.2%) to urgent care units and 32 (21.2%) were hospitalised (not mutually exclusive events). In 64 children with FW or RP in non-FHS areas these figures were: 56 (87.5%), 50 (78.1%) and 11 (17.2%), respectively.

Vaccination cards were recovered for 89.2% of children (813/911) but many cards were incomplete (many had had more than one card and had lost the first one). The vaccination coverage rate was: 97.4% (n=777) with BCG in 798 children with data, and 84.2% (n=659) for any dose of *Haemophilus influenza* type B vaccine in 783 children. There was no difference in vaccination coverage between FHS and non-FHS areas. Given the poor household record and high coverage rate, vaccination was not further analysed.

Variables for social network showed poor internal consistency (Cronbach's alpha for each variable < 0.60 and for all variables = 0.418) and thus were excluded from further analysis. Internal consistency was considered satisfactory for social support (alpha for each variable > 0.7 and for all variables = 0.737), and therefore the sum of the scores was combined in one dichotomous variable

("low" when the sum ≤10 and "high" sum >10) based on visual inspection. The data on family income were considered unreliable and not analysed.

There was no difference in duration of **breastfeeding and smoking**. The proportions of children aged ≥ 9 months that were breastfed for ≥ 9 months were 48.9% in FHS and 49.9% in non-FHS areas (data not shown in tables). The proportions of children whose mother smoked were 22.0% in FHS and 23.6% in non-FHS areas. Thirty-three percentage of children (33.0%) of children in FHS and 33.6% in non-FHS areas were currently living with other smokers living in the same house and that were not their mothers.

Distribution of risk factors between FHS and non-FHS areas

Table 8 below shows the results from a descriptive bivariable analysis comparing potential risk factors between FHS and non-FHS areas for the 6 variables selected in the last multivariable models (CCA and MI). **Table 9** shows results for the last multivariable model analyses, with CCA and with MI including the 6 variables whose P value was ≤0.10 in either analysis. Families in FHS areas had a higher proportion of houses with mould, piped water, daily garbage collection, mother who had someone who helped with childcare, and mother with previous deceased child. In contrast, FHS areas had fewer people per house.

Table 8: Results from the descriptive bivariable analysis comparing potential risk factors between FHS and non-FHS areas for variables selected in the last multivariable model.

Variables		Bivariable analysis				Total
		FHS areas N=612		Non-FHS areas N=299		
		n	%	n	%	
Presence of mould	Yes	500	81.7	221	73.9	721
	No	104	17.0	76	25.4	180
	Missing	8	1.3	2	0.7	10
Number of people in the house	3-4	287	46.9	109	36.5	396
	≥5	264	43.1	146	48.8	410
	Missing	61	10.0	44	14.7	105
Piped water in the house of people in the house	Yes	522	85.3	201	67.2	723
	No	85	13.9	96	32.1	181
	Missing	5	0.8	2	0.7	7
Garbage collection	Every day	500	81.7	221	73.9	721
	Once a week or more	104	17.0	76	25.4	180
	Missing	8	1.3	2	0.7	10
Mother had another child who died	Yes	72	11.8	17	5.7	89
	No	531	86.8	279	93.3	810
	Missing	9	1.5	3	1.0	12
Other person who helped to take care the child	Yes	359	58.7	140	46.8	499
	No	252	41.2	150	50.2	402
	Missing	1	0.2	9	3.0	10

FHS and non-FHS: areas covered and not covered by family health system

Table 9: Results of the multivariate analysis based on complete casa analysis and with imputed data, comparing FHS and non-FHS areas (reference group). Unit of analysis is the household.

Variables	Complete case analysis N=581[1]						Analysis with imputed data N = 759 [2]	
	Areas				OR (95%CI) [3]	P	OR (95%CI) [3]	P
	FHS		Non-FHS					
	N	%	N	%				
Presence of mould								
No (reference)	171	43	115	64	1		1	
Yes	231	57	64	36	2.49 (1.71; 3.63)	<0.001	2.57 (1.42; 4.64)	0.005
Number of people in the house								
5+ (reference)	178	48	97	54	1		1	
3-4	224	56	82	46	1.65 (1.14; 2.41)	0.009	2.00 (1.10; 3.62)	0.027
Piped water in the house								
No (reference)	62	15	55	31	1		1	
Yes	340	85	124	69	2.42 (1.56; 3.73)	<0.001	2.21 (0.53; 9.23)	0.247
Garbage collection								
Once a week or more (reference)	63	16	40	22	1		1	
Every day	339	84	139	78	1.63 (1.01; 2.61)	0.044	1.16 (0.27; 4.94)	0.800
Other person who helped to take care the child								
No (reference)	169	42	93	52	1		1	
Yes	233	58	86	48	1.59 (1.08; 2.31)	0.018	1.76 (1.10 2.80)	0.023
Mother had another child who died								
No (reference)	361	90	166	93	1		1	
Yes	41	10	13	7	1.74 (0.87; 3.45)	0.115	3.91 (1.25; 12.21)	0.024

FHS and non-FHS: areas covered and not covered by family health system.

Notes: [1] Results from unweighted multivariable analyses, adjusted for all variables in the table but no adjustment for clustering, p = 0.517 for Hosmer Lemeshow test; [2] Results from weighted multivariable analyses, adjusted for all variables in the table with adjustment for clustering (ACS as cluster), excluding 4 children in their families because they had doubtful address; [3] comparing the prevalence of the risk factor in FHS households over households in non-FHS areas. For example, an unadjusted analysis on presence of mould: odds ratio = (231*115)/(171*64) = 2.43.

Table 10 below shows results for bivariable analysis comparing the frequency of potential risk factors for the 3 categories of LRD and reference category, only for the 6 variables selected in the last multivariable models (CCA and MI). **Table 11** below presents the results for the last model of the multivariable analyses for CCA and MI (variables with P value ≤0.10 in either analysis). The factors associated with higher proportion of mild wheezers were presence of maternal asthma and child's age < 1 year. For frequent wheezers the associated factors were maternal asthma, had had pets recently and child´s age > 1 year. Duration of exclusive breastfeeding was not associated with MW or FW. The RP in either analysis the associated factors were: presence of maternal smoking, had had pets recently pets, shorter duration of total breastfeeding, child´s age ≥ 1 year and low score for social support.

Table 10. Results from the descriptive bivariable analysis comparing the frequency of potential risk factors for the 3 categories of lower respiratory disease and reference category, only for variables selected in the last multivariable models.

Variables		Categories for lower respiratory disease							
		Reference (no disease)		Mild wheezer		Frequent wheezer		Referred pneumonia	
		n	%	n	%	n	%	n	%
Maternal smoking	Never	370	77.7	164	74.5	134	77.0	27	65.9
	Stopped recently	56	11.8	23	10.5	17	9.8	9	22.0
	Yes, currently	43	9.0	28	12.7	21	12.1	5	12.2
	Missing	7	1.5	5	2.3	2	1.1	0	0.0
Total breastfeeding	0-1 months	72	15.1	27	12.3	27	15.5	14	34.1
	2-6 months	156	32.8	81	36.8	54	31.0	7	17.1
	≥ 7 months	231	48.5	102	46.4	87	50.0	19	46.3
	Missing	17	3.6	10	4.5	6	3.4	1	2.4
Maternal asthma	Yes	47	9.9	40	18.2	36	20.7	6	14.6
	No	411	86.3	179	81.4	134	77.0	35	85.4
	Missing	18	3.8	1	0.5	4	2.3	0	0.0
Presence of pets	Never	284	59.7	119	54.1	95	54.6	20	48.8
	Has now	165	34.7	89	40.5	61	35.1	17	41.5
	Had recently	11	2.3	6	2.7	14	8.0	4	9.8
	Missing	16	3.4	6	2.7	4	2.3	0	0.0
Child's age	< 1 year	86	18.1	54	24.5	20	11.5	4	9.8
	≥ 1 years < 2 years	91	19.1	43	19.5	46	26.4	16	39.0
	≥ 2 years	299	62.8	123	55.9	108	62.1	21	51.2
	Missing								
Social support	High	14	2.9	11	5.0	11	6.3	6	14.6
	Low	446	93.7	204	92.7	158	90.8	35	85.4
	Missing	16	3.4	5	2.3	5	2.9	0	0.0

Table 11: Multivariable analyses for the association between potential risk factors and lower respiratory disease

Variables	Complete case analysis N=699[1]			Analysis with in	
	Association OR (95% CI)				Associatio
	Mild wheezer	Frequent wheezer	Referred pneumonia	Mild wheezer	Fr w
Maternal smoking					
Never (reference)	1	1	1	1	
Stopped recently	0.93 (0.50; 1.76)	0.88 (0.45; 1.73)	2.75 (1.07; 7.07)	1.31 (0.69; 2.50)	0.74 (
Yes, currently	1.73 (0.96; 3.11)	1.34 (0.70; 2.56)	1.55 (0.48; 4.96)	1.68 (0.72; 3.91)	1.10 (
Total breastfeeding					
0-1 months (reference)	1	1	1	1	
2-6 months	1.09 (0.61; 1.94)	0.79 (0.43; 1.47)	0.28 (0.10; 0.78)	1.24 (0.62; 2.48)	0.85 (
≥ 7 months	1.11 (0.64; 1.94)	1.03 (0.58; 1.83)	0.41 (0.17; 0.96)	1.37 (0.74; 2.56)	1.04 (
Maternal asthma					
No (reference)	1	1	1	1	
Yes	1.89 (1.12; 3.17)	2.59 (1.53; 4.38)	1.43 (0.49; 4.16)	1.87 (1.04; 3.38)	3.18 (
Presence of pets					
Never (reference)	1	1	1	1	
Has now	1.26 (0.85; 1.85)	1.13 (0.74; 1.72)	1.20 (0.54; 2.66)	1.33 (0.99; 1.78)	1.07 (
Had recently	0.99 (0.33; 2.97)	3.46 (1.47; 8.14)	4.21 (1.12; 15.84)	1.66 (0.37; 7.46)	2.33 (
Child's age					
< 1 year (reference)	1	1	1	1	
≥ 1 years < 2 years	0.84 (0.47; 1.50)	2.46 (1.22; 4.97)	4.63 (1.19; 18.04)	0.59 (0.35; 1.02)	1.86 (
≥ 2 years	0.65 (0.41; 1.04)	1.74 (0.93; 3.26)	1.69 (0.45; 6.32)	0.53 (0.33; 0.84)	1.75 (
Social support					
High (reference)	1	1	1	1	
Low	1.96 (0.82; 4.71)	2.20 (0.92; 5.27)	4.11 (1.32; 12.84)	2.79 (0.81;9.60)	1.92 (

Notes:

[1] Results from unweighted multivariable analyses, adjusted for all variables in the table and no adjustment for clustering, p = 0.837 for

[2] Results from weighted multivariable analyses, adjusted for all variables in the table and with adjustment for clustering (mothers as clu

Table 12: Summary of the results of the two analyses: Households in FHS over non-FHS areas (analysis 1), and individuals with lower respiratory disease over individuals without disease (analysis 2)

Potential risk factors	Analyses							
	Analysis 1		Analysis 2					
			Mild wheezer		Frequent wheezer		Referred pneumonia	
	Results		Results		Results		Results	
	CCA	MI	CCA	MI	CCA	MI	CCA	MI
Presence of mould	⬆	⬆	–	–	–	–	–	–
Fewer number of people in the house	⬆	⬆	–	–	–	–	–	–
Presence of piped water in the house	⬆	⇧	–	–	–	–	–	–
Daily garbage collection	⬆	⇧	–	–	–	–	–	–
Presence of other person who helped to take care the child (over absence)	⬆	⇧	–	–	–	–	–	–
Mother had another child who died (over with not having had died who died)	⬆	⇧	–	–	–	–	–	–
Currently maternal smoking (over never smoked)	–	–	⇧	⇧	⇧	⇧	⇧	⇧
Total breastfeeding (2-6 months over 0-1 month)	–	–	1	⇧	⇩	⇩	⬇	⇩
Maternal asthma	–	–	⬆	⬆	⬆	⬆	⇧	⇧
Presence of pets (had recently over never)	–	–	1	⇧	⬆	⇧	⬆	⇧
Child's age (≥ 1 years < 2 years over < 1 year)	–	–	⇩	⇩	⬆	⇧	⬆	⬆
Social support (low compared with high)	–	–	⇧	⇧	⇧	⇧	⬆	⬆

Complete case analysis (CCA) and multiple imputations (MI)

Notes: ⬆ increased prevalence and statistically significant, ⇧ increased without significance; ⬇ decreased prevalence and statistically significant, ⇩ decreased without significance; **1** association measure closes to 1; "–" variables not used in multivariable analyses; statistically significance if $P < 0.05$.

Discussion

Main findings. The results can be summarised in three main findings. **First**, more than 50% of the children in the study population had lower respiratory disease with wheeze (MW and FW) and the proportion of children with disease was higher FHS areas than in non-FHS areas, but without statistically significance. MW was more frequent: weighted prevalence varied from 21% to 25%, FHS areas and non-FHS, respectively. The same figures for FW were 15% to 19%. **Secondly**, the potential risk factors for LRD were more frequent in families living in FHS than in non-FHS. **Third**, at individual level, the factors associated with higher prevalence of LRD were maternal smoking, less duration of breastfeeding, maternal asthma, presence of pets, child´s age ≥ 1 year, and low social support.

On the prevalence of LRD. We consider that the prevalence of LRD found in this study was not different of other estimates in the country. Fr example, the highest prevalence of frequent wheezers found in this study population, corresponding to the most specific definition of asthma, was 19.1%, while the prevalence of recurrent wheezing (≥ 3 episodes) in other study varied between 22% and 36% in infants (Mallol 2010).

Risks factors associated with LRD. Prevalence was lower if the house had pets that were recently removed from the house, what could be explained by reverse causation: Once that a child has the disease, the pet is removed from the house. Alternatively, the presence of pets decreases the risk of asthma. But the direction of this association is still controversial (Lodge 2012). Association between low social support and prevalence of wheezing disorder was found and it has also been previously described elsewhere (Santos 2012). In this study, the results suggest that the lower the social support, the higher the probability of pneumonia and/or that the wheezing disorder progresses to more severe cases (referred pneumonia).

Can environmental intervention reduce the prevalence of wheezing disorder (WD)? Modifiable environmental conditions can be involved in the causation of WD (Mallol 2013) and thus, even interventions not directed to its control may change the occurrence of disease. Three factors were found associated with wheezing disorder and can be considered as potentially modifiable by the FHS: breastfeeding, maternal smoking and presence of pets. However, they were not differently distributed between the two areas. Among the factors distributed differently between the two areas,

only presence of mould could be considered as modifiable according to the literature, but it was not associated with the outcome in the multivariable analyses.

The prevalence of LRD was similar in the two areas. We consider three explanations. Firstly, the current ACS´ routine activities have not modified the exposure of risk and/or protective modifiable factors enough to impact in the risk of disease. Indeed, activities of the ACSs focus on interventions addressing some specific diseases (e.g., diabetes and hypertension) (Johnson 2013), but there is no a set of actions targeting specifically the control of respiratory disease. Secondly, there are other important risk factors or aetiology that are not be modifiable or the risk changed by the ACS activities, for example, bronchiolitis due to virus infection specially among infants (Pereira 2007), and therefore the prevalence rate would not be reduced. A third explanation is that the current activities have had some effects in reducing the frequency of disease, but other interventions with similar effects had already been implemented in non-FHS areas and therefore making the prevalence rates of LRD similar in the two areas. In such contiguous urban areas under the same health administration, the activities with potential to prevent respiratory disease could have had implemented similarly and had similar impact in the two areas. For example, Brazil has a successful campaign to reduce tobacco smoking (Levy 2012), and maybe both areas were equally under the influence of these campaigns.

Prevention of WD. This study measured prevalence and prevalence is in function of incidence and duration of disease. Therefore, the effects of ACS activities could reduce the incidence (primary prevention), reduce the duration/severity (control of disease), or both. Primary prevention is controversial and probably needs a "multifaceted approach" given the multifactorial characteristic of the disease (Chan-Yeung 2006). However, the activities of the ACS could potentially reduce risk factors and/or to promote protective factors. For example, breastfeeding has been demonstrated to be negatively associated with asthma, despite controversy remains (Kramer 2014). In Brazil, it has been described successful experience with the training of ACS aimed to a further increase of breastfeeding (Coutinho 2014), as well as a study in the Netherlands (Schonberger 2005). But in this study, there was no difference between areas regarding breastfeeding, and breastfeeding was similar to the 49.9% found in the survey in 2008 in the same metropolitan region for children aged 9-12 months (Ministerio da Saude-Brasil 2009.). Other action could be the reduction of exposure to environmental tobacco smoke, but tobacco exposure was similar in both areas.

The fact that the study involved contiguous areas could also suggest that the children could be exposed to similar outdoor environmental conditions not modifiable by ACS activities. There is evidence that most cases with wheezing disorder in Brazil are non-atopic and related to poor environmental conditions (Pereira 2007; Cunha 2010a). The study site of this survey had poor sanitation, absence of pavement, large amount of garbage in the streets, stray animals and frequent flooding with open sewage. If the frequency of wheezing disorder is mainly determined by these factors, the primary prevention is not feasible by the ACSs. The causes for non-atopic wheezing are not completely understood and may depend on improvements in public infrastructure which goes well beyond individuals' activities.

Another intervention is the control of asthma symptoms that can involve modifiable factors, such as smoking cessation (Wright 2014). Mould, in which has been also found associated with the prevalence of asthma in Brazil (Azalim 2014), seems to be more related to exacerbations than as a cause of disease (Douwes 2003). Mould was found in 49.6% of the houses in this study. However, interventions against mould would include from periodically cleaning of walls to removal of water-damaged materials and repairs in the houses (Sauni 2011), and in this study mould was associated with the outcome only in the univariable analysis. Therefore, it is unclear whether changes in mould would lead to changes in the prevalence of disease in this study setting. Despite some successful experiences with removal and elimination of pests (Bryant-Stephens 2009), it is also doubtful whether these interventions are feasible in areas similar in this survey: many study areas could be better described as shantytowns.

Maybe more promising intervention is the Programme called "The Asthma Child program" aimed to provide a better care and broader access to free medications for patients with wheezing at primary care services, including inhaled corticosteroids to reduce the frequency and severity of exacerbations. In Brazil, it has been demonstrated effective in decreasing hospitalization rates and visits in emergency departments (Fontes 2011). This is run by the local governments and includes health education and indoor environmental control against asthma triggers. But there are scarce data so far about their effectiveness on prevention of the disease where these educational measures have been adopted in Brazil, although there is evidence that they can be effective in other countries (Turcotte 2014). In this survey, children in FHS areas had a higher proportion of children whose doctors mentioned "asthma" as a diagnosis and prescribed bronchodilators, what could suggest higher quality care in FHS areas, but this is offset by the fact that similar proportion sought emergency units

and hospitalization in comparison with non-FHS areas, and therefore there is still room to improve the quality of care for those with more severe disease.

The results in this survey should be interpreted with some cautions. This is a cross-sectional study with limitations in assessing causal associations (Reichenheim 2010). Selection bias cannot be excluded, since areas initially selected had to be excluded in the field work (unit nonresponse) and less than 80% of the study sample could be used in a multivariable analysis due to missing data (aggregate rate of missing data), even though we applied multiple imputation to deal with bias due item nonresponse.

It is worth emphasising that results from complete case analysis and multiple imputation (MI) are based on two different assumptions and only MI analyses were weighted, therefore are not duplications of information and not necessary should have the same results. Another caution is related to sparse data when analysing referred pneumonia. Definition of asthma case in epidemiologic studies can be difficult and misclassification bias can exist. Diagnosis by using questionnaires is mostly based on the presence of "shortness-of-breath", cough, wheeze, "bronchitis", and asthma diagnosed by a doctor (Tennant 2003), as used in this study. In the reference group (n=476), there were 264 with no symptoms, 207 children only with cough, 1 child only with "shortness-of-breath" and 4 with both symptoms. Therefore, the reference group did not represent those without any respiratory symptom. However, it would be highly unlikely that children without one of these two symptoms had "asthma" or LRD, at most they could have clinical manifestation below the threshold that can be recognized by a questionnaire. However, if all the 4 children with both symptoms and 1 only with "shortness-of-breath" had "asthma", the misclassification bias would be negligible because these 5 children were only 1.1% of the total of 476 children in this group. By the contrary, we think that the use of only those with no symptoms (n=264) to represent the reference group would be more likely to cause selection bias because they were 55% of 476. The questionnaire was applied in specific months in the year of 2011 but the outcome was measured as 12-month period prevalence of symptoms and there is no empirical evidence suggesting bias (Stewart 1997). Generalization of these results should also be done carefully as respiratory diseases are also determined by environmental factors that vary in different populations, and that not all populations have community health workers.

We suggest that more research should be done to promote real evidence based information to guide health policy decisions. In our opinion, whether the control measures already described in the

literature could be adapted to the context of the FHS, be effective and feasible, is a relevant issue.

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