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To cite this article: Javier Mallol, Dirceu Solé, Viviana Aguirre, Herberto Chong, Nelson Rosario, Luis García-Marcos & EISL Study Group (2017): Changes in the prevalence and severity of recurrent wheezing in infants: The results of two surveys administered 7 years apart, Journal of Asthma, DOI: [10.1080/02770903.2017.1403625](https://doi.org/10.1080/02770903.2017.1403625)

To link to this article: <https://doi.org/10.1080/02770903.2017.1403625>



Published online: 12 Dec 2017.



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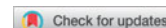
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Changes in the prevalence and severity of recurrent wheezing in infants: The results of two surveys administered 7 years apart

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ABSTRACT

Objective: To identify changes in the prevalence and severity of recurrent wheezing (RW) in infants using data obtained from two surveys administered seven years apart. **Methods:** A cross-sectional, international, population-based study in infants aged 12–15 months was conducted. Data were obtained from two surveys (S1 and S2, in 2005 and 2012, respectively) using the same methodology in three large Latin American cities: Curitiba (Brazil), São Paulo (Brazil), and Santiago (Chile). **Results:** A decrease in the overall prevalence of RW was identified between S1 (23.3%) and S2 (20.4%), $p = 0.004$, but it was mainly driven by the reduction observed in São Paulo; in Curitiba and Santiago, this change was not significant. The mean prevalence of the following RW severity indicators remained high and stable: severe wheezing episodes (56.9% in S1 and 54.2% in S2, $p = 0.32$) and emergency department (ED) visits for wheezing (S1 = 68.1%, S2 70.9%, $p = 0.21$). A significant increase in admissions for wheezing (21.1% to 26.7%, $p = 0.004$) was observed. In Curitiba and São Paulo, there were significant increases in the prevalence of physician-diagnosed asthma and in the use of inhaled corticosteroids and oral antileukotrienes. **Conclusions:** The prevalence and severity of RW during the first year of life remained high over time, with remarkably high rates of ED visits, admissions for wheezing and use of asthma medications. This study suggests the need for considering early asthma diagnosis and to establish an appropriate treatment in infants with recurrent and severe asthma-like symptoms.

ARTICLE HISTORY

Received 13 May 2017
Revised 1 November 2017
Accepted 7 November 2017

KEYWORDS

Pediatrics; epidemiology; prevention; treatment

Introduction

Recurrent wheezing (RW), defined as three or more physician-diagnosed episodes of wheezing, is one of the most important clinical manifestation of asthma in infants. RW places a major burden on both parents and national health systems because of the high rates of consultations, medical facility use, admissions, medication prescription, and comorbidities associated with this condition [1–3]. Large cross sectional, population-based international studies in infants aged 12–15 months from Latin America and Europe, have found high prevalence rates of RW, severe episodes of wheezing, ED visits, and hospital admissions for wheezing during the first year of life [3,4]. However, the temporal changes in the prevalence of those variables in Latin America are unknown.

This could be important in terms of public health because our previous finding of a high prevalence, severity, and related morbidity of RW in this region [3]. It is likely that knowing temporal trend of this condition could be useful for implementing, monitoring, and evaluating community-level health interventions aimed at reducing prevalence and severity of RW. We hypothesized that as occurs with the prevalence of asthma in schoolchildren [5–7], the temporal changes in the prevalence and severity of RW in infants could vary among centers showing an increase, a decline or no changes. In that case, mean changes from several centers would not represent the actual trend of prevalence and severity at each locality.

To our knowledge, no published data are available regarding temporal changes in the prevalence and

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severity of RW during the first year of life in large samples of infants at the international scale. The latter may be important because infants who suffer from RW may be at an increased risk of asthma and lung function impairment in late childhood and adulthood [8–12]. Recently, a large nation-wide study in the USA which analyzed asthma trends among children aged 0–17 years from 2001 to 2013, found that in the group aged 0–4 years there was a decrease in the prevalence of asthma at the end of the study period [13].

The present study compares changes in the prevalence and severity of RW in infants, among others related variables, between two surveys that were administered at the same Latin American centers in Brazil (Curitiba and São Paulo) and Chile (Santiago) 7 years apart using the same methodology.

Methods

The present study compares data on prevalence, severity, and other related variables, of RW in infants from two surveys (S1 and S2) carried out in 2005 and 2012, respectively. For S1 and S2, study samples were obtained from populations living in the same defined geographical areas (centers) in Curitiba (Brazil), São Paulo (Brazil) and Santiago (Chile); these centers were selected for data comparisons because they participated in 2005 and 2012. The main points for comparisons between S1 and S2 were the changes in RW prevalence, indicators of RW severity (severe episodes, ED visits, and admissions for wheezing) and the use of asthma medications. Secondly we assessed changes in the prevalence of common cold, pneumonia, and admission for pneumonia in infants with RW.

Both surveys are part of the Estudio Internacional de Sibilancias en Lactantes (EISL) (International Study of Wheezing in Infants in English) which is a multicountry, multicentric, cross-sectional, population-based study that has been carried out using the same methodology in all involved centers. Its main objective is to assess the prevalence and severity of and risk factors and use of medications for RW in randomly sampled infants during the first year of life; detailed EISL methods have been described elsewhere [3,4]. Briefly, random samples of infants aged 12–15 months were recruited from primary care clinics where infants are taken by their parents for growth/development monitoring and/or vaccine administration. A standardized questionnaire on wheezing that also included questions on risk/protective factors, such as common respiratory infections (URTI, colds), pre- and postnatal tobacco exposure, infant eczema, parental asthma, and day-care attendance; severe episodes; ED visits and admissions for wheezing was used. The rates of,

inhaled short-acting beta two agonists (SABA), inhaled corticosteroid (ICS) and leukotriene receptor antagonist (LTRA) use in the studied sample of infants were also evaluated. For the purposes of this study, infants with RW and parental asthma were considered at higher risk of later asthma [14,15]. The prevalence of RW, physician-diagnosed asthma, ED visits and admissions for wheezing, and use of asthma medication, among others, was assessed in the three participating centers in 2005 and 2012 to determine the pattern of observed changes, on average and at each participating center. The required sample sizes were calculated as follows: if the real prevalence of RW during the first year of life was 20% in one center and 15% in another, samples of approximately 800 individuals per center would provide 80% power to detect a true difference at a significance level of 5%.

This study was approved by the Scientific Ethics Committee, Chilean Ministry of Health, Southern Metropolitan Area of Santiago de Chile (Chile), and the respective ethics committees of the participating Brazilian centers. Parents or guardians who agreed to participate in the study filled out the questionnaire after reading and signing a full-informed written consent form.

Data analysis

The changes in prevalence and severity of RW, and in other related factors, occurred between S1 and S2 in the three participating cities were compared using statistical software (SPSS V.15, Chicago, IL, USA and MedCalc V.17.8, Ostend, Belgium). The chi-squared test was used to compare proportions between S1 and S2, and $p < 0.05$ was considered statistically significant. In general, the results are expressed as the mean and 95% confidence interval (95% CI); age is reported as the mean and standard deviation (SD). Adjusted multivariate logistic regression analyses were performed to evaluate associations, which are expressed as odd ratios and 95% CIs.

Results

The three participating centers provided 7,003 questionnaires in S1 (Curitiba = 3,003, São Paulo = 1,012 and Santiago = 2,988), and 3,206 in S2 (Curitiba = 980; São Paulo = 892 and Santiago = 1,334). The mean response rates were 88.3% for S1 and 85.6% for S2; the mean ages of the whole sample of infants were 12.8 ± 1.1 months for S1 (50.9% male) and 13.1 ± 1.3 months for S2 (51.6% male). The parental questionnaire response rates were 91.6% (84.0% mother) for S1 and 93.3% (85.1% mother) for S2. Changes identified between the surveys in the prevalence of wheezing and related factors in the whole sample of infants and infants with RW in the three cities are shown

Table 1. Changes in the prevalence rates ($\Delta\%$) of variables related to wheezing during the first year of life in the whole sample of infants during the 7-year period between S1 and S2 in Curitiba, São Paulo and Santiago.

Whole sample of Infants	Curitiba				Santiago				São Paulo			
	S1	S2	$\Delta\%$	p	S1	S2	$\Delta\%$	p	S1	S2	$\Delta\%$	p
Tobacco use during pregnancy	14.0	9.3	-4.7	0.000	8.8	10.8	2.0	0.08	15.6	11.4	-4.2	0.004
Passive tobacco exposure	42.1	24.6	-17.5	0.000	43.7	50.6	6.9	0.000	38.4	27.2	-11.2	0.000
Maternal tobacco use	21.6	20.6	-1.0	0.54	32.4	34.4	2.0	0.28	19.4	14.8	-4.6	0.004
Wheezing: ≥ 1 episode	45.1	39.5	-5.6	0.002	63.2	58.6	-4.6	0.014	46.0	44.6	-1.4	0.53
Wheezing during the first 3 months	13.6	8.9	-4.7	0.000	25.1	17.7	-7.4	0.000	17.4	15.5	-1.9	0.24
RW	22.6	19.7	-2.9	0.06	22.7	20.4	-2.3	0.16	26.8	21.7	-5.1	0.005
Severe wheezing episode: ≥ 1	20.9	13.5	-7.4	0.000	23.0	22.5	-0.5	0.79	22.3	19.3	-3.0	0.08
ED visits for wheezing	26.1	19.4	-6.7	0.000	29.7	26.8	-2.9	0.10	29.3	29.5	0.2	0.95
Admissions for wheezing	5.7	3.9	-1.8	0.035	8.3	6.4	-1.9	0.08	9.1	14.5	5.4	0.000
SABA use	38.4	33.7	-4.7	0.009	63.6	57.2	-6.4	0.001	39.6	43.4	3.8	0.07
ICS use*	8.3	12.9	4.6	0.000	18.8	16.1	-2.7	0.08	5.4	16.0	10.6	0.000
LTRA use†	2.4	11.8	9.4	0.000	2.0	1.7	-0.3	0.68	1.2	4.1	2.9	0.000
Physician-diagnosed asthma	4.9	5.6	0.7	0.43	2.9	2.6	-0.3	0.72	3.5	9.7	6.2	0.000
Parental asthma	17.7	13.2	-4.5	0.012	9.5	9.5	0.0	0.95	8.1	17.4	9.3	0.95
Parental rhinitis	45.9	47.1	1.2	0.54	14.1	19.3	5.2	0.000	37.1	40.6	3.5	0.09
Sibling asthma	10.3	4.2	-6.1	0.000	6.5	6.2	-0.3	0.81	5.1	5.3	0.2	0.90
Pneumonia	12.3	9.1	-3.2	0.008	18.0	13.9	-4.1	0.005	18.6	17.2	-1.4	0.41
Admission for pneumonia	6.0	3.9	-2.1	0.015	9.4	6.1	-3.3	0.003	8.6	10.3	1.7	0.19
Cold during the first 3 months	33.6	31.4	-2.2	0.24	44.2	36.0	-8.2	0.000	32.9	29.9	-3.0	0.14
Colds ≥ 6 times during the first year	25.7	25.2	-0.5	0.80	24.2	23.5	-0.7	0.71	27.7	19.9	-7.8	0.000
Tobacco use during pregnancy	14.0	9.3	-4.7	0.000	8.8	10.8	2.0	0.08	15.6	11.4	-4.2	0.004
Passive tobacco exposure	42.1	24.6	-17.5	0.000	43.7	50.6	6.9	0.000	38.4	27.2	-11.2	0.000
Maternal tobacco use	21.6	20.6	-1.0	0.54	32.4	34.4	2.0	0.28	19.4	14.8	-4.6	0.004
Breast feeding for 4 or more months	69.5	67.8	-1.7	0.35	79.7	76.3	-3.4	0.035	62.7	56.4	-6.3	0.003
Maternal education: high [§]	39.3	64.7	25.4	0.000	56.4	58.6	2.2	0.26	41.1	51.2	10.1	0.000
Nursery attendance	24.9	23.4	-1.5	0.37	7.3	12.8	5.5	0.000	19.6	40.4	20.8	0.000
Maternal employment: yes	46.3	57.4	11.1	0.000	25.2	27.1	1.9	0.28	45.1	66.4	21.3	0.000

RW, recurrent wheezing; ED, emergency department; SABA, inhaled short-acting beta two agonists; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonists. *ICS were not available without cost to parents at the primary care level during S1 in São Paulo; †, LTRAs were not available without cost to parents at the primary care level at the time of S1 or S2 in any of the 3 centers; §, more than 12 years of education.

in Tables 1 and 2. In this section, we will mainly report the findings identified in infants with RW; changes in the whole sample of infants are depicted in Table 1.

Changes in RW prevalence

There was a significant decrease in the mean prevalence of RW between S1 (23.3%; 95% CI 22.3–24.3) and S2 (20.4%; 95% CI 19.0–21.8), $p = 0.004$; however, this significance was driven by the decreased prevalence identified in São Paulo. The mean prevalence of wheezing during the first 3 months of life also decreased between surveys, declining from 50.2% (95% CI 47.8–52.6) to 43.4% (95% CI 39.7–47.2) in S1 and S2, respectively, $p = 0.004$; again, this difference was driven by the decrease observed only in São Paulo. The mean change in the proportion of infants who had ≥ 7 episodes of wheezing during the first year of life was not significant, $p = 0.89$, (Table 1).

Indicators of RW severity

There was no significant change in the mean prevalence of severe episodes of wheezing between S1 (56.6%; 95% CI 54.2–59.0) and S2 (54.2%; 95% CI 50.4–58.0), $p = 0.077$; however, the prevalence of this indicator significantly decreased in Curitiba but not in Santiago or

São Paulo. The increase identified in the mean prevalence of ED visits for wheezing between S1 (68.1%, 95%; CI 65.8–70.3) and S2 (70.9%, 95%; CI 67.4–74.3) was not significant, with Curitiba showing a significant decrease, São Paulo a significant increase and Santiago a non-significant decrease. There was a significant increase in the mean prevalence of admissions for wheezing between S1 (21.1%; 95% CI 19.2–23.2) and S2 (26.7%; 95% CI 23.4–30.2), $p = 0.004$, which was mainly driven by São Paulo, which showed a 1.8-fold increase. (Table 2).

There was a significant increase in the mean prevalence of physician-diagnosed asthma between S1 (13.3%; 95% CI 11.7–15.0) and S2 (21.8%; 95% CI 18.9–25.1), $p < 0.001$; this increase was significant in São Paulo (2.7-fold) and Curitiba (1.4-fold) but not in Santiago.

The mean proportion of infants at risk of asthma (RW plus parental asthma) demonstrated a non-significant increase between S1 (18.8%; 95% CI 17.0–20.9) and S2 (23.6%; 95% CI 25.9–37.0), $p = 0.28$; however, there was a significant increase in São Paulo (2.3-fold), $p = 0.001$ (Table 2).

Common colds

The mean prevalence of colds during the first 3 months of life significantly decreased between S1 (57.9%; 95% CI 55.4–60.3) and S2 (50.7%; 95% CI 46.9–54.5), $p = 0.029$

Table 2. Changes in the prevalence rates ($\Delta\%$) of variables related to wheezing during the first year of life in infants with RW during the 7-year period between S1 and S2 in Curitiba, São Paulo and Santiago.

Infants with RW	Curitiba				Santiago				São Paulo			
	S1	S2	$\Delta\%$	p	S1	S2	$\Delta\%$	p	S1	S2	$\Delta\%$	p
Wheezing during the first 3 months	40.2	31.1	− 9.1	0.027	61.0	52.7	− 8.3	0.05	48.3	45.7	− 2.6	0.60
At risk for later asthma*	26.2	24.4	− 1.8	0.70	13.2	12.6	− 0.6	0.93	13.3	30.1	16.8	0.000
Severe wheezing episode: ≥ 1	59.4	42.5	− 16.9	0.000	55.1	59.9	4.8	0.28	53.5	58.5	5.0	0.27
ED visits for wheezing	69.2	57.5	− 11.7	0.003	65.5	69.8	4.3	0.32	71.6	80.6	9.0	0.016
Admissions for wheezing	17.1	11.9	− 5.2	0.10	24.3	19.2	− 5.1	0.18	23.2	41.2	18.0	0.000
SABA use	89.5	86.0	− 3.5	0.22	98.7	99.5	0.8	0.61	88.9	98.6	9.7	0.000
ICS use**	23.8	41.0	17.2	0.000	55.6	51.2	− 4.4	0.39	15.9	46.9	31.0	0.000
LTRA use‡	7.0	37.1	30.1	0.000	4.1	4.8	0.7	0.88	3.0	15.2	12.2	0.000
Physician-diagnosed asthma	16.2	23.3	7.1	0.030	11.3	8.8	− 2.5	0.41	10.7	29.1	18.4	0.000
Parental asthma	26.2	24.4	− 1.8	0.012	13.2	12.6	− 0.6	0.93	13.3	30.1	16.8	0.000
Parental rhinitis	54.3	47.2	− 7.1	0.09	17.7	19.8	2.1	0.59	42.1	46.4	4.3	0.36
Sibling asthma	14.2	6.3	− 7.9	0.005	12.5	13.7	1.2	0.77	6.6	11.1	4.5	0.09
Pneumonia	26.1	22.3	− 3.8	0.33	42.6	35.2	− 7.4	0.09	38.7	40.1	1.4	0.80
Admission for pneumonia	15.2	10.4	− 4.8	0.12	24.3	17.0	− 7.3	0.047	17.3	24.9	7.6	0.036
Cold during the first 3 months	51.5	47.2	− 4.3	0.35	67.7	63.0	− 4.7	0.27	48.8	45.1	− 3.7	0.44
Colds ≥ 6 times during the first year	54.5	46.0	− 8.5	0.05	59.9	55.8	− 4.1	0.38	56.0	47.8	− 8.2	0.07
Tobacco use during pregnancy	19.5	11.4	− 8.1	0.013	11.2	14.8	3.6	0.23	21.8	19.0	− 2.8	0.47
Passive tobacco use	47.5	28.0	− 19.5	0.000	48.2	50.5	2.3	0.64	47.2	36.3	− 10.9	0.011
Maternal tobacco use	25.0	26.9	1.9	0.77	35.1	35.2	0.1	0.95	25.1	23.5	− 1.6	0.73
Breast feeding for 4 or more months	63.2	62.4	− 0.8	0.91	73.8	71.5	− 2.3	0.604	55.4	56.1	0.7	0.94
Maternal education: high ^{§, **}	31.9	65.3	33.4	0.000	55.5	60.4	4.9	0.27	38.0	48.4	10.4	0.08
Nursery attendance	34.3	36.3	2.0	0.67	13.0	23.1	10.1	0.001	29.9	52.2	22.3	0.000
Maternal employment: yes	45.3	62.1	16.8	0.000	28.4	34.1	5.7	0.16	46.1	70.2	24.1	0.000

RW: recurrent wheezing; ED: emergency department; SABA: inhaled short-acting beta two agonists; LTRA, leukotriene receptor antagonists.

*RW plus parental asthma [16]; **, ICS were not available without cost to parents at the primary care level during S1 in São Paulo; ‡, LTRAs were not available without cost to parents at the primary care level at the time of S1 or S2; §, more than 12 years of education.

which was mainly driven by Santiago; similarly, the mean prevalence of experiencing ≥ 6 colds during the first year of life significantly decreased between S1 (57.0%; 95% CI 54.5–59.5) and S2 (49.4%; 45.6–53.2), $p = 0.024$.

Pneumonia and admissions for pneumonia in infants with RW

No significant change was identified between the prevalence of pneumonia reported on S1 (35.1%) and S2 (33.6%), $p = 0.52$. Similarly, the mean prevalence of pneumonia admissions did not decrease significantly between S1 (19.3%) and S2 (18.5%), $p = 0.70$. The results of the logistic regression analysis (adjusted for sex, birth weight, parental asthma, and tobacco use during pregnancy) showed that RW was strongly associated with reported pneumonia (S1 OR 3.5; 95% CI 3.9–5.2, $p < 0.001$; S2 OR 4.7; 95% CI 3.8–5.8, $p < 0.001$) and admissions for pneumonia (S1 OR 4.8; 95% CI 3.9–5.8, $p < 0.0001$, and S2 OR 4.5; 95% CI 3.35–5.92, $p < 0.001$).

Medications

There was a significant increase in the overall use of LTRAs (3.8-fold) between S1 (5.1%; 95% CI 4.1–6.3) and S2 (19.5%; 95% CI 16.4–23.1), $p = 0.007$; this increase was significant in Curitiba (3.9-fold increase) and São Paulo (4.6-fold increase) but not in Santiago.

The use of ICS in infants with RW increased significantly between S1 (36.6%; 95% CI 33.3–38.0) and S2 (46.3%; 95% CI 42.5–50.3), $p = 0.003$, which was driven by increases in Curitiba (1.7-fold increase) and São Paulo (2.9-fold increase); Santiago had a non-significant decrease. The use of SABA remained similar in Curitiba and Santiago but increased significantly in São Paulo. (Table 2)

Among infants with a higher risk of asthma (RW and parental asthma), there was a significant increase in the mean use of ICS between S1 (34.0%; 95% CI 28.8–39.7) and S2 (57.6%; 95% CI 49.6–65.2), $p = 0.002$. The proportions of infants with RW treated only with SABA by disease prevalence and severity (Table 3) indicated the presence of an overall significant decrease, but a high proportion of infants with severe RW were reported to be only treated with SABA on S2 (41.0%; 95% CI 35.5–46.8). Concomitantly, the percentage of infants with RW treated with SABA plus ICS significantly increased in São Paulo, from 17.0% to 47.4%, $p = 0.0006$, and Curitiba, from 25.6% to 47.8%, $p = 0.0008$, while in Santiago there was a non-significant decrease from 55.7% to 51.5%, $p = 0.47$.

Discussion

Changes in prevalence and severity

This is the first international, cross sectional, population-based study to assess over time changes in the prevalence

Table 3. Proportion (%) of infants with RW treated with inhaled SABA as a single treatment in the evaluated centers at both survey timepoints (S1 and S2).

	Only SABA S1 % (95% CI)	Only SABA S2 % (95% CI)	p between S1 and S2
RW (≥ 3 episodes)			
Curitiba	63.3 (59.6–66.9)	36.8 (29.8–44.4)	<0.001
São Paulo*	72.7 (67.1–77.7)	45.7 (39.9–51.6)	<0.001
Santiago	42.9 (39.2–46.6)	47.2 (39.9–54.5)	0.49
Wheezing ≥ 7 episodes			
Curitiba	59.2 (53.1–64.9)	28.8 (18.8–41.38)	<0.001
São Paulo	71.0 (61.5–79.0)	42.3 (33.3–51.9)	0.017
Santiago	27.7 (21.6–34.7)	20.0 (11.0–34.8)	0.65
Severe wheezing episode ≥ 1			
Curitiba	60.9 (56.1–65.6)	27.0 (18.2–38.1)	0.003
São Paulo	69.0 (61.0–75.9)	47.1 (39.8–54.5)	0.003
Santiago	33.7 (29.1–38.6)	45.8 (36.2–55.8)	0.153
ED visits for wheezing			
Curitiba	60.6 (56.2–64.9)	30.8 (22.9–40.1)	0.001
São Paulo	74.2 (67.6–79.9)	45.5 (39.0–52.3)	<0.001
Santiago	35.7 (31.4–40.3)	46.5 (38.0–55.1)	0.146
Admissions for wheezing			
Curitiba	53.4 (44.4–62.3)	40.0 (23.4–59.3)	0.431
São Paulo	68.3 (56.0–78.4)	47.9 (38.2–57.8)	0.053
Santiago	15.2 (10.5–21.4)	31.9 (20.4–46.2)	0.220

*ICS were not available without cost to parents at the primary care level during S1 in São Paulo.

RW: recurrent wheezing; ED: emergency department; SABA: inhaled short-acting beta two agonists.

and severity of RW and use of health care facilities and anti-asthma medications in infants during the first year of life, using comparable populations (same centers) and methodology. The results of this study showed that prevalence of RW and severity indicators for RW (such as severe episodes, ED visits, and admissions for wheezing) remained particularly high, even after 7 years. The prevalence and severity of RW increased in some centers whereas in others declined or did not change, which agrees with our hypothesis. This suggests that besides reporting the average change in prevalence for centers, the pattern of changes among them should be also reported as this information would allow to surmise the differences existing among centers, for instance with respect to the management of infants with frequent and severe wheezing.

Previous studies [3,4] have reported that approximately 2 out of every 10 infants at the community level suffer from RW, resulting in a remarkable demand for medical consultations, use of health facilities, and prescription medication. This finding is quite like the longitudinal overtime variation in the prevalence of asthma symptoms in older children reported by the International Study of Asthma and Allergies in Childhood (ISAAC) [5–7], which identified heterogeneity in the changes (upward or downward) in current asthma prevalence, even in centers within a same country, with a general trend to increasing in less affluent regions. A recent large population-based study on the trends in asthma prevalence using 2001–2013 National Health Interview Survey data for children aged 0–17 years in the USA, suggests that overall prevalence of asthma in children has ceased

increasing by the end of the study period [13]; however, there were diverse asthma trends in the same study period for the different age groups, poverty status groups, geographic regions, and race/ethnicities. For instance, in the group aged 0–4 years there was a decrease in the prevalence of asthma at the end of the study period whereas in the group aged 10–17 the prevalence increased.

In the present study, and irrespective of variations between the prevalence rates of wheezing and associated factors observed within the three cities, the overall patterns in the severity of the condition did not change substantially, with high rates of severe episodes, ED visits, and admissions for wheezing. These findings suggest that the factors affecting the prevalence and severity of RW have remained stable over time in evaluated locations despite alleged improvements in the accessibility of better health care and anti-asthma treatments at the community level in recent years. We speculate that the high prevalence of severe wheezing identified among those with RW was the main factor responsible for the notable use of health facilities, ED visits, and medications, such as ICS, oral corticosteroids, and antibiotics, as previously shown [3,4]. Although in the present study, we found that the mean prevalence of RW in the three cities decreased by 2.7% (from 23.4 to 20.7%) during the 7 years of study, is worth noting that this change was mainly driven by the larger decrease observed in the prevalence of RW in São Paulo, a decrease that did not occur in Santiago and Curitiba. We do not have a clear explanation for the obvious decrease in RW prevalence that occurred in São Paulo or for the relatively stable prevalence rates of RW in Santiago and Curitiba over the course of seven years.

Several factors might be involved; of these factors, the fact that ICS were available for free in primary care facilities in São Paulo at the time of S2 but not at the time of S1 may be of importance. The decreases noted in the prevalence of colds during the first trimester of life, the prevalence of six or more colds during the first year of life, and pre- and postnatal exposure to tobacco in some of the study centers may have also played a role, as these are well-known risk factors for RW [16,17]. Other factors not assessed by the present study may have also influenced the prevalence of RW, including increased understanding of the meaning of wheezing or bronchial obstruction episodes among patients and changes in the labeling of lower respiratory episodes; accessibility to medical care and inhaled asthma medications; environment (air pollution, incidence and severity of viral respiratory infections, socioeconomic status, etc.) and physicians' diagnostic (labeling) and treatment preferences. We do not know why the prevalence of colds in the first three months of life decreased only in Santiago and not in the other centers, or why the decrease in RW prevalence and increase in admissions for wheezing occurred only in São Paulo. It might be related with environmental aspects and yearly variations in the rates of illness, pathogens involved, and other random epidemiological variations of viral respiratory infections. However, a causal relationship is not possible to determine because of the study design (cross-sectional).

Change in medications

The increase observed in the use of ICS in Curitiba (1.7-fold) and São Paulo (3.0-fold) and the remarkable increase identified in the use of LTRAs in these centers (Curitiba (3.9-fold increase) and São Paulo (4.6-fold increase) were concordant with the increased prevalence of physician-diagnosed asthma. This difference likely reflects a move toward more frequently diagnosing asthma in infants with RW; a corresponding increase in the prescription of anti-asthma medications was identified in Curitiba and São Paulo. Furthermore, increases in the use of ICS would be in line with the evidence and guidelines supporting the use of ICSs as first line treatments for asthma symptoms in preschool children [18–21]. However, the marked increase in the prescription of LTRAs for infants with RW in São Paulo and Curitiba, where 15% and 37% of the infants with RW received LTRA at the time of S2, respectively, is difficult to explain. It might reflect adherence to guidelines or the physicians' therapeutic options, although current evidence does not support the use of montelukast in preschool children with RW [22–25]. Besides, this medication is not free of adverse effects, such as the mental health effects previously reported in children [26,27].

The results of this study show that a high proportion of infants with RW (even those with ≥ 7 episodes and troublesome progression) continued to receive SABA as a single treatment approach. This finding may be one of the potential explanations for why the prevalence and severity of RW remained high and stable in the three studied centers, even after 7 years. Supporting this hypothesis is the finding that 42% of infants who met major criteria (RW plus parental asthma) for the initiation of control therapy with ICS, as recommended by major guidelines [19,20], were not treated accordingly.

Our study confirms previous data on the markedly increased risk of pneumonia and admission for pneumonia in infants with RW [3,4], particularly in infants who began wheezing during the first three months of life (X-ray pneumonia), as previously found in a birth cohort in Santiago de Chile [28].

The similar findings identified in the two surveys allowed the magnitude of the impact of RW during the first year of life on public health to be estimated, the results of which implied the presence of a sustained and large health system burdens and, most likely, serious impairment to the quality of life of infants and their parents. This observation clearly indicates the necessity of implementing better diagnostic and treatment strategies for infant with troublesome recurrent asthma symptoms and effective and transversal educational programs for health personnel and parents. Based on our findings, it appears necessary to improve diagnostic labeling to change the old paradigm that asthma does not exist in infants. The EISL studies [3,4] have been the first to provide evidence from tens of thousands of infants suggesting that a high proportion of those with RW (without physician-diagnosed asthma) were treated with ICS and other medications. Our findings may be helpful to convince governmental health institutions to allocate proper resources for the treatment of asthma in infants at the primary care level in our region. Double-blind, randomized and placebo-controlled trials have shown that ICS are effective and safe in controlling symptoms and improving lung function in Latin American infants with RW [29,30]. Thus, when used as recommended (regularly and with monitoring for inhalation technique, dose adjustment, and adherence), these medications might have a beneficial impact on the prevalence rates of severe episodes, ED visits, and hospital admissions in infants with RW; however, this hypothesis remains to be proven by longitudinal studies.

Strengths and limitations

Cross-sectional studies, such as the present study, are methodologically restricted in their utility when assessing causality, the effect of medications, as well as other

factors. We used parent-reported instead of physician-reported wheezing, which may be a limitation; however, we employed a previously validated questionnaire that has demonstrated good agreement [31–33]. The effects of unknown variations in respiratory viruses and other environmental changes during the 7 years between surveys on prevalence and severity may also be a limitation. The strengths of the present study include its large randomly selected population-based sample, high response rate and use of same methods and centers in both surveys. Overall, this study is the first to provide comparative information regarding longitudinal trends in the prevalence and severity of RW in infants, comorbidities, and the diagnostic and therapeutic options employed by physicians in different centers.

This knowledge may be useful when designing public health strategies and distributing resources for the management of this condition at the community level, particularly in developing countries. These findings call for the development of public health initiatives directed at early prevention. Some protective and risk factors for RW, such as tobacco use in pregnancy, early viral respiratory infections (first trimester of life) and breast feeding [16,17], *may be feasibly modified*.

Conclusions

The results of the present study show that the prevalence and severity of RW during the first year of life remain high, varying in direction and magnitude among participating centers over the course of the 7 years that separated S1 and S2. The rate of asthma diagnosis in infants who met the criteria for being at high risk of asthma, i.e., RW and parental asthma, was low, which supports the notion that this condition is underdiagnosed and under-treated. A high proportion of infants with severe RW still were only treated using SABA. This study also suggests the need to improve diagnostic and therapeutic strategies for the management of infants with asthma symptoms; this necessity is particularly emphasized by the high prevalence of severe episodes observed in infants with RW and its therapeutic management. Our results highlight the necessity of rethinking asthma in infants together with implementing effective and standardized regional educational programs for parents and health personnel. Perhaps these initiatives may help to decrease the prevalence, severity of progression and associated morbidities in infants with RW in Latin America.

Acknowledgements

We are grateful to the parents who participated in the International Study of Wheezing in Infants (EISL) and their infants;

additionally, we are appreciative of the valuable collaboration and assistance provided by the staff of the primary health centers in each participating country.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Author contributions

All authors participated in the conception and design of the study; collection, analysis, and interpretation of the data; drafting and revision of the manuscript; and approval of final version of the manuscript.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that the study procedures were performed in accordance with the regulations of the responsible Clinical Research Ethics Committee, the World Medical Association, and the Helsinki Declaration.

Confidentiality of data

The authors declare that no patient data appear in this article.

Right to privacy and informed consent

The authors declare that no patient data appear in this article.

Funding

No funding was granted for this study.

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