

ORIGINAL ARTICLE: ASTHMA

Healthcare utilization in infants and toddlers with asthma-like symptoms

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Funding information

Clalit Health Services, Grant/Award Number: none; Clalit Research Institute

Abstract

Background: Recurrent asthma-like symptoms are common in infants, but few population studies describe diagnostic and treatment practice.

Methods: Using the electronic data repository of Clalit Health Services, the largest integrated health care provider in Israel, we evaluated children born 2005–2012, who before 3 years of age had >3 episodes of asthma-like symptoms and/or >2 bronchodilator purchases within a year. We described health care utilization and the odds ratio for subsequent utilization after 3 and 12 months' controller therapy. The primary outcome measure was respiratory-related doctor visits. Linear and categorical regression analysis measured overall effectiveness of therapy.

Results: Among 689 171 infants, 262 900 (38.1%) had > 3 asthma-like episodes/year during at least 1 year. Of those, 26 108 (10%) purchased controller therapy: 20 316 (77.8%) inhaled corticosteroids (ICS) with or without leukotriene receptor antagonists (LTRA), and 5792 (22.2%) LTRA alone. For these 26 108 over 3 months there were 93 845 respiratory-related doctor visits, 3110 hospital admissions, 5568 diagnoses of pneumonia, 9960 chest X-rays, 37 127 purchases for oral steroids, and 45 142 for antibiotics courses. Healthcare utilization decreased following ICS ± LTRA and LTRA alone, respectively, as follows: doctor visits 7% and 3%, chest X-rays 16% and 17%, bronchodilators 20% and 11%, systemic steroids 17% and 12%, and antibiotics by 35% and 22%, ($P < .001$ for all). Twelve months' therapy remained effective.

Conclusions: Asthma-like symptoms are common in infants. Health care utilization is very high and physician practices should be reassessed. Following controller therapy, health care utilization decreased. Yet controllers were prescribed in only a minority of eligible children.

KEYWORDS

asthma, controller treatment, health care utilization, infantile asthma, infants, inhaled corticosteroids, leukotriene receptor antagonists, preventive therapy, wheezing

1 | INTRODUCTION

Abbreviations: API, Asthma Predictive Index; ICS, Inhaled Corticosteroids; LTRA, Leukotriene receptor antagonists; SES, Socioeconomic status.

One in three children experiences at least one acute wheezing episode before the age of 3 years,¹ though not all develop persistent

asthma.^{2,3} Nonetheless, infants with recurrent episodes of wheezing or other asthma-like symptoms may experience severe exacerbations requiring systemic glucocorticoids and bronchodilators, along with frequent use of health care services.⁴ Inhaled glucocorticoids (ICS) and leukotriene receptor antagonists (LTRA) are the preferred asthma controller therapies, according to the Global Initiative for Asthma (GINA) guidelines.^{5,6} However, while some studies, including the START study and a meta-analysis by Castro-Rodriguez et al,^{7,8} have shown that ICS are efficacious in children under the age of 5 years, others, such as the Danish Pediatric Asthma center's study, Clavenna, and the ENBe Study Group have failed to demonstrate short-term efficacy.^{9,10}

There are no large cohort studies of infants and toddlers measuring the real-world effectiveness of controller therapy on asthma-related symptoms or health care utilization. We used electronic medical records from Clalit Health Services (CHS), the largest single health care system in Israel, to evaluate the level of health care utilization in this population and the effectiveness

of controller therapy in reducing asthma-related health care utilization.

2 | METHODS

2.1 | Study design

This historical prospective study compared health care utilization before and after the introduction of controller therapy among self-matched children born between 2005 and 2012 who had asthma-like symptoms and initiated controller therapy before age of 3 years (Figure 1). We compared outcomes pretreatment (control group) vs posttreatment (case group), for 3 and 12 months of therapy duration.

Our eligibility criteria were based on the GINA 2017 guidelines,⁶ which recommend daily ICS treatment for children with uncontrolled asthma or more than three exacerbations per year, described as "a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough." We therefore included children with at

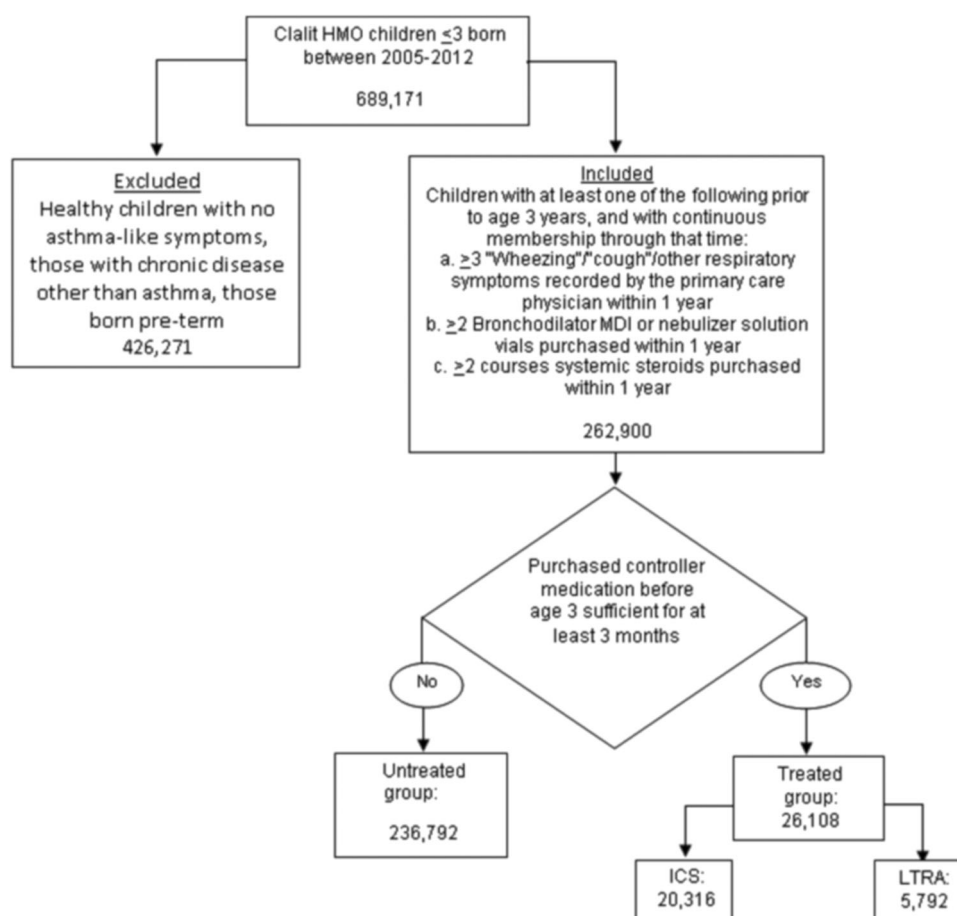


FIGURE 1 Study population: the algorithm for enrolling the study groups, presented as a flow chart. Of all children with asthma-like symptoms, children were considered as using controller therapy if they purchased at least 3 months of consecutive therapy. With regard to ICS, this included fluticasone propionate, 50 to 125 µg/dose, 100 doses/metered dose inhaler (MDI), >2 MDIs within 3 months, and >4 inhalers for 1 year; beclomethasone dipropionate, 50 to 100 µg/dose, 200 doses/MDI, >1 inhaler within 3 months, and >3 inhalers for 1 year; budesonide nebulizer: >60 nebulizers of 1 mg each within 3 months and >180 amps for 1 year; The LTRA prescribed was Montelukast 4 mg/pill or sachet, >56 pills/sachets within 3 months, and >168 doses for 1 year. ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist

least one of the following: (a) three or more asthma-like symptoms, defined as episodes of "wheezing," "dyspnea," "bronchitis," or "asthma" recorded by the primary care physician (defined as a "respiratory" visit) within 1 year; (b) two or more bronchodilator metered dose inhalers or nebulizer solution vials purchased within 1 year (as each MDI has 125-200 doses, we considered that two inhalers would likely represent therapy for three or more episodes); (c) two or more courses of systemic steroids purchased within 1 year. These inclusion criteria were similar to other large population asthma and health care usage studies.¹¹

We excluded children with other pre-existing conditions require systemic steroid therapy, those who were born prematurely, and those who were not continuously members of CHS from birth through 3 years of age.

2.2 | Context

Data were extracted from the CHS database. As the largest integrated health care provider and insurer in Israel, CHS covers over half of the national population and has a centralized database warehouse collating clinical and administrative data from most medical encounters of all members. To protect the privacy of CHS members, deidentified data are analyzed in aggregate form. The study was approved by the CHS institutional review board.

2.3 | Exposure

Children were considered as using controller therapy if they purchased at least 3 months of consecutive therapy as defined by GINA guidelines.⁶ This was calculated to provide at least 50% of treatment required for this period, as the least required for symptom control.¹² With regard to ICS, this included fluticasone propionate, 50 to 125 µg/dose, 100 doses/metered dose inhaler (MDI), >2 MDIs within 3 months, and >4 inhalers for 1 year; beclomethasone dipropionate, 50 to 100 µg/dose, 200 doses/MDI, >1 inhaler within 3 months, and >3 inhalers for 1 year; budesonide nebulizer: >60 nebulizer treatments of 1 mg each within 3 months and >180 ampules for 1 year; the LTRA prescribed was montelukast 4 mg/pill or sachet, >56 pills/sachets within 3 months, and >168 doses for 1 year. Children who used both ICS and LTRA (any amount) during the course of the study were designated to the ICS group.

2.4 | Outcome measures

The primary outcome measure was the number of respiratory-related doctor visits. The secondary outcome measures were number of respiratory-related hospital admissions, pneumonia diagnoses (doctor diagnosis according to ICD-9 486.0), chest radiographs, and use of the following pharmaceutical therapy: bronchodilators including salbutamol MDI or nebulizer solution, terbutaline nebulizer solution, oral steroids, and antibiotics (penicillin and its derivatives or macrolides and their derivatives). We began measuring outcomes

from 30 days following the initiation of controller therapy, when treatment was most likely to have achieved its full effect.¹³

2.5 | Covariates

Baseline demographics included sex (male or female), socioeconomic status ([SES] low, medium, or high, defined by the clinic catchment area), ethnicity (Arab, Orthodox Jewish, or other, also as defined by the clinic catchment area), and residence (rural or urban). Socioeconomic status was estimated based on the primary care clinic's designation, calculated by CHS based on available data of the mean socioeconomic status of the neighborhood, as determined by the Israeli Central Bureau of Statistics, and graded into three strata, low, medium, and high.

Additional data evaluated included the recorded age and season (April-August or September-March) of the first respiratory symptom, age at initiation of controller therapy, reported smoking by either parent, and having a positive modified asthma predictive index (API).^{14,15} The modified API was defined for this study as at least one of the following: eosinophils >4% or 500/µL absolute eosinophil count from routine screening at 9 to 15 months of age; diagnosis of atopic dermatitis, food allergy or allergic rhinitis; or parents with a diagnosis of asthma or >2 purchases for bronchodilators as a sign of parental asthma. These were the features of API that were available from the patients' electronic records.

2.6 | Analysis

Baseline demographics and risk factors for children with asthma-like symptoms were compared with children without such symptoms. Among those with asthma-like symptoms, we compare baseline demographics and risk factors between those who did and did not go on to receive controller therapy. Then, by each outcome, we compared the number, rate, and average change 3 months before and 3 months after the initiation of controller therapy. We also conduct analyses of outcomes among patients who had 12 months of therapy and 12 months of follow-up.

Linear regression analysis was used while adjusting for potential significant covariates for continuous outcomes, and logistic regression was used for dichotomous outcomes. Unadjusted and adjusted odds ratios (OR) were calculated for each outcome.

We also compared categorical factors between groups by χ^2 test, and for continuous distributions by Student *t* test. Statistical significance was defined by a two-sided alpha level of .05 and 95% confidence intervals for odds ratios were calculated. All analyses were performed using SPSS version 23 (IBM Armonk, NY).

3 | RESULTS

This analysis included 689 171 infants and toddlers who were born between 2005 and 2012. Among them, 262 900 (38%) had asthma-like symptoms before age three according to GINA 2017 guidelines.

TABLE 1 Total cohort characteristics and demographics stratified by the inclusion criteria of having asthma-like symptoms

Characteristic		Total N (%)	Nonwheezers N (%)	Wheezers N (%)	P value* (wheezers vs nonwheezers)
		689 171 (100%)	426 271 (61 0.9%)	262 900 (38.1%)	<.001
Sex	Male	352 867 (51.20%)	202 689 (47.50%)	150 178 (57.1%)	<.001
	Female	335 750 (48.70%)	223 045 (52.30%)	112 705 (42.9%)	<.001
	Missing	554 (0.08%)	537 (0.13%)	17 (0.0%)	
SES	Low	309 075 (49.4%)	175 563 (47.3%)	133 512 (50.8%)	<.001
	Medium	212 278 (33.9%)	126 633 (34.2%)	85 645 (32.6%)	<.001
	High	104 447 (16.7%)	68 611 (18.5%)	35 836 (13.6%)	<.001
	Missing	63 371 (9.2%)	55 464 (13.0%)	7907 (3.0%)	
Ethnicity	Arab	209 631 (31.7%)	118 321 (29.5%)	91 310 (35.0%)	<.001
	Orthodox Jews	45 387 (6.9%)	33 134 (8.3%)	12 253 (4.7%)	<.001
	Nonorthodox Jews	406 999 (61.5%)	249 609 (62.2%)	157 390 (60.3%)	<.001
	Missing (%)	26 854 (3.9%)	25 028 (5.9%)	1826 (0.7%)	
Residence	Rural	84 352 (12.80%)	57 942 (14.50%)	26 410 (10.0%)	<.001
	Urban	576 410 (87.20%)	341 984 (85.50%)	234 426 (89.2%)	<.001
	Missing	28 409 (4.10%)	26 345 (6.20%)	2064 (0.8%)	
Smoking by either parent	Yes	265 549 (42.2%)	156 827 (40.5%)	108 722 (41.4%)	<.001
	No	364 104 (52.8%)	230 802 (54.1%)	133 302 (50.7%)	<.001
	Missing	59 518 (8.6%)	38 642 (9.1%)	20 876 (7.9%)	
Season of first respiratory symptom	April-August	146 835 (21.3%)	77 104 (18.1%)	69 731 (26.5%)	<.001
	September-March	413 084 (59.9%)	221 354 (51.9%)	191 730 (72.9%)	<.001
	Missing	129 252 (18.7%)**	127 813 (30%)**	1439 (0.5%)	
Age at first respiratory symptom	Mo (mean[SD])	7.1 (6.3)	8.3 (7.1)	5.5 (4.6)	<.001

Abbreviations: SES, socioeconomic status; SD, standard deviation.

*Total cohort characteristics and demographics stratified by the inclusion criteria of having asthma-like symptoms or not. χ^2 test was done for statistical analysis for all categorical characteristics except for age for which t test was used. P value indicates significant differences between the wheezers and the nonwheezers children.

**No respiratory symptoms documented for many of the nonwheezers group.

Demographic features and risk factors comparing those with and without asthma-like symptoms are shown in Table 1.

Preanalysis showed that children with asthma-like symptoms who did not receive controller therapy were significantly different in all parameters from those who received therapy, suggesting that these groups were not comparable and possibly had a different severity of illness. Therefore, subsequent analyses were restricted to the cohort of children who received the controller therapy.

Children with asthma-like symptoms were more likely to be males, of a lower SES, living in an urban environment, and with parents who smoked. The age of onset of the first respiratory symptom was lower for those with recurrent asthma-like symptoms. As expected, the first respiratory symptom occurred mainly in the fall and winter seasons for all populations. Of note, many children within the group of nonwheezers had no respiratory symptoms documented till the age of 3 years.

Of those children with asthma-like symptoms, 26 108 (10%) received controller therapy; 20 316 (78%) received ICS with or without LTRA, and 5792 (22%) received LTRA alone. Table 2 reports the characteristics of these children according to the treatment group.

There were significantly more males than females in both treatment groups as compared with the untreated group ($P < .001$). Children in the untreated group were more likely to come from a low SES, whereas more in the ICS and LTRA groups came from a medium SES. Most children were nonorthodox Jewish, but this was more pronounced in those treated with ICS.

The percentage of parents who smoked was higher in the ICS treated group. There was no difference among groups regarding the week of birth or weight at birth.

Treated infants had their first respiratory symptom at a younger age than the untreated infants. The season of the first asthmatic symptom was similar for both treatment groups. Modified API

TABLE 2 Patient with asthma-like symptoms characteristics and demography stratified by controller therapy

Characteristic		ICS treatment N (%)	LTRA treatment N (%)	No treatment N (%)	P value* (treated vs not treated)
		20 316 (7.7%)	5792 (2.2%)	236 792 (90.1%)	< .001
Sex	Male	12 765 (62.8%)	3690 (63.7%)	133 723 (56.5%)	<.001
	Female	7550 (37.2%)	2102 (36.3%)	112 705 (42.9%)	<.001
	Missing	1 (0.0%)	0 (0.0%)	16 (0.0%)	
SES	Low	6153 (30.3%)	2265 (39.1%)	125 094 (52.8%)	<.001
	Medium	9026 (44.4%)	2378 (41.1%)	74 241 (31.4%)	<.001
	High	4702 (23.1%)	1052 (18.2%)	30 082 (12.7%)	<.001
	Missing	435 (2.1%)	97 (1.7%)	7375 (3.1%)	
Ethnicity	Arab	2348 (11.6%)	1290 (22.3%)	87 596 (37.0%)	<.001
	Orthodox Jews	759 (3.7%)	104 (1.8%)	10 831 (4.6%)	<.001
	Nonorthodox Jews	17 208 (84.7%)	4398 (75.9%)	136 526 (57.7%)	<.001
Residence	Rural	2525 (12.4%)	664 (11.5%)	23 221 (9.8%)	
	Urban	17 774 (87.5%)	5125 (88.5%)	211 527 (89.3%)	<.001
	Missing	17 (0.1%)	3 (0.1%)	2044 (0.9%)	<.001
Either parent smoking	Yes	9060 (44.6%)	2322 (40.1%)	97 340 (41.1%)	<.001
	No	10 303 (50.7%)	2761 (47.7%)	120 238 (50.8%)	<.001
	Missing	953 (4.7%)	709 (12.2%)	19 214 (8.1%)	
Season of first respiratory symptom	April-August	5633 (27.7%)	1670 (28.8%)	62 428 (26.4%)	<.001
	September-March	14 672 (72.2%)	4074 (70.3%)	172 984 (73.1%)	<.001
	Missing	11 (0.1%)	48 (0.8%)	1380 (0.6%)	
Age at first respiratory symptom	Mo (mean[SD])	4.7 (3.4)	4.7 (3.9)	5.5 (4.7)	<.001
Age at first dose ICS	Mo (mean[SD])	10.0 (5.9)	11.4 (6.2)	14.2 (8.1)	<.001
Modified API	Positive	15 141 (76.4%)	4241 (76.1%)	158 419 (71.3%)	<.001
	Negative	4690 (23.6%)	1331 (23.9%)	63 653 (28.7%)	<.001
	Missing	485 (2.4%)	220 (3.8%)	14 720 (6.2%)	

Abbreviations: API, Asthma Predictive Index; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; SES, socioeconomic status; SD, standard deviation.

*Wheezing infants characteristics stratified by controller treatment. χ^2 test was done for statistical analysis for all categorical characteristics except for age for which t test was used. P value indicates significant differences between the treated and not treated children.

documented positive for more treated children compared with the nontreated group.

3.1 | Outcomes: health care utilization

Table 3 describes health care utilization, medication purchased, and pneumonia diagnosis in those children that received controller therapy. Absolute numbers of the outcomes are shown 3 and 12 months before and after, compared with after institution of asthma controller medication.

Before therapy, health care utilization was extremely high. For example, over 3 months, 20 264 infants before ICS controller therapy had 70 880 doctor visits, 28 310 purchases for systemic steroids, and 33 709 purchases for antibiotics. Treatment with ICS or LTRA for 3 months was associated with a significant ($P < .001$) reduction in the rates of all health care services utilization, medications purchase, and pneumonia diagnosis,

although most remained high. The rate of children that visited the doctor for respiratory reasons decreased from 99% to 92% using ICS and from 96% to 93% using LTRA. The most impressive decline was in chest imaging rates (32%-16% using ICS and from 30% to 13% using LTRA), and systemic steroids purchase (57%-40% using ICS and from 59% to 47% using LTRA). Other health care utilizations rates decreased: hospital admissions (11%-8% using ICS and from 8% to 6% using LTRA), pneumonia diagnosis (15%-11% using ICS and from 9% to 7% using LTRA), bronchodilators purchase (91%-71% using ICS and from 85% to 74% using LTRA), macrolide (57%-49% using ICS and from 61% to 57% using LTRA), and penicillin (41%-30% using ICS and from 43% to 36% using LTRA).

Only 3634 (17.9% of children receiving ICS controller therapy) continued to 12 months usage of ICS, and only 1036 (18.1% of children receiving LTRA controller therapy) continued LTRA for 12 months.

TABLE 3 Changes in absolute numbers of health care services and medications purchases

A. Three months before and following the initiation of controller medications						
Controller treatment	ICS treatment			LTRA treatment		
Number of infants on controller	20 263			5714		
Outcomes in numbers	3 Mo pre	3 Mo post	P value*	3 Mo pre	3 Mo post	P value*
Doctor visits	70 880	62 480	<.001	22 965	15 332	<.001
Hospital admissions	2 588	1 785	<.001	522	367	<.001
Pneumonia diagnosis	4 822	3 509	<.001	746	601	.004
Chest X-rays	7 952	4 039	<.001	2 008	846	<.001
Bronchodilators	28 533	24 003	<.001	8 726	6 447	<.001
Systemic steroids	28 310	20 363	<.001	8 817	5 989	<.001
Macrolide	20 953	18 540	<.001	7 251	6 181	<.001
Penicillin	12 756	9 506	<.001	4 182	3 308	<.001
B. Twelve months before and following the initiation of controller medications						
Controller treatment	ICS treatment			LTRA treatment		
Number of infants on controller	3634			1036		
Outcomes in numbers	12 Mo pre	12 Mo post	P value*	12 Mo pre	12 Mo post	P value*
Doctor visits	30 259	18 503	<.001	8 518	7 530	<.001
Hospital admissions	395	366	.37	67	147	<.001
Pneumonia diagnosis	2101	849	<.001	206	150	.058
Chest X-rays	1911	127	<.001	446	55	<.001
Bronchodilators	12 186	5 560	<.001	3 330	2 134	<.001
Systemic steroids	9 044	4 382	<.001	2 336	1 638	<.001
Macrolide	8 082	6 146	<.001	2 300	2 049	<.001
Penicillin	4 871	2 332	<.001	1 402	845	.045

Note: Data was included only for those children continuing controller therapy over the 12 month period.

Abbreviations: ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist.

*Absolute numbers of the outcomes measured, comparing treated vs not treated children. The t test was done for statistical analysis. P value throughout indicates significant differences between the treated children paired before vs during the treatment.

Similar findings with ICS therapy for 12 months, with an even more dramatic reduction in chest imaging rates (34% rates to 3% following 12 months' of ICS treatment; 30%-5% with LTRA) and systemic steroids purchases (57%-39%). Furthermore, diagnoses of pneumonia dropped more significantly following the initiation of 12 months treatment (26%-13%). The rates for doctor visits reduced from 98% to 94% during the treatment, bronchodilator (91%-72%), macrolides (68%-59%), and penicillin (53%-32%) reduced as well, but not hospitalizations (from 9% to 8% but P-value not significant), when using ICS for 12 months.

As for the LTRA treatment most outcomes improved, although the improvement was slightly less than with ICS for 3 months, except for the reduction in chest imaging which the most prominent decline following 12 months treatment with LTRA (30%-5%). LTRA was effective in reducing most parameters. Doctor visits (94%-92%), bronchodilators purchase (88%-75%), systemic steroids purchase (56%-52%), and penicillin purchase (51%-40%). However, the rate of hospitalization was higher during 12 months treatment (6% increased to 12%), although numbers were small. Also, macrolides purchases slightly increased (64%-65%) but without statistical

significance. Pneumonia diagnosis reduced from 10% to 9% but without statistical significance.

Figure 2 demonstrates the reduction in health care services utilization, medication purchased, and pneumonia diagnosis, comparing ORs of usage/purchase/diagnosis for each child pre vs post initiation of asthma controller medication.

ORs for all outcomes measured after 3 months' treatment were <1 for both ICS and LTRA controller therapy. The best ORs were for doctor visits (0.13) during the ICS treatment, and chest imaging (0.35) for the LTRA treatment.

Unlike the findings following a short period of preventive treatment with LTRA, ORs after 12 months treatment were more than 1 for hospital admissions (2.16) and minimally, for penicillin purchase (1.07). The most striking reduction in OR was for chest imaging (0.06 and 0.11) with both ICS and LTRA treatment.

Table 4 demonstrate the reduction in health care services utilization, medication purchased and pneumonia diagnosis, comparing mean usage/purchase/diagnosis for each child pre versus post initiation of asthma controller medication and the difference between them.

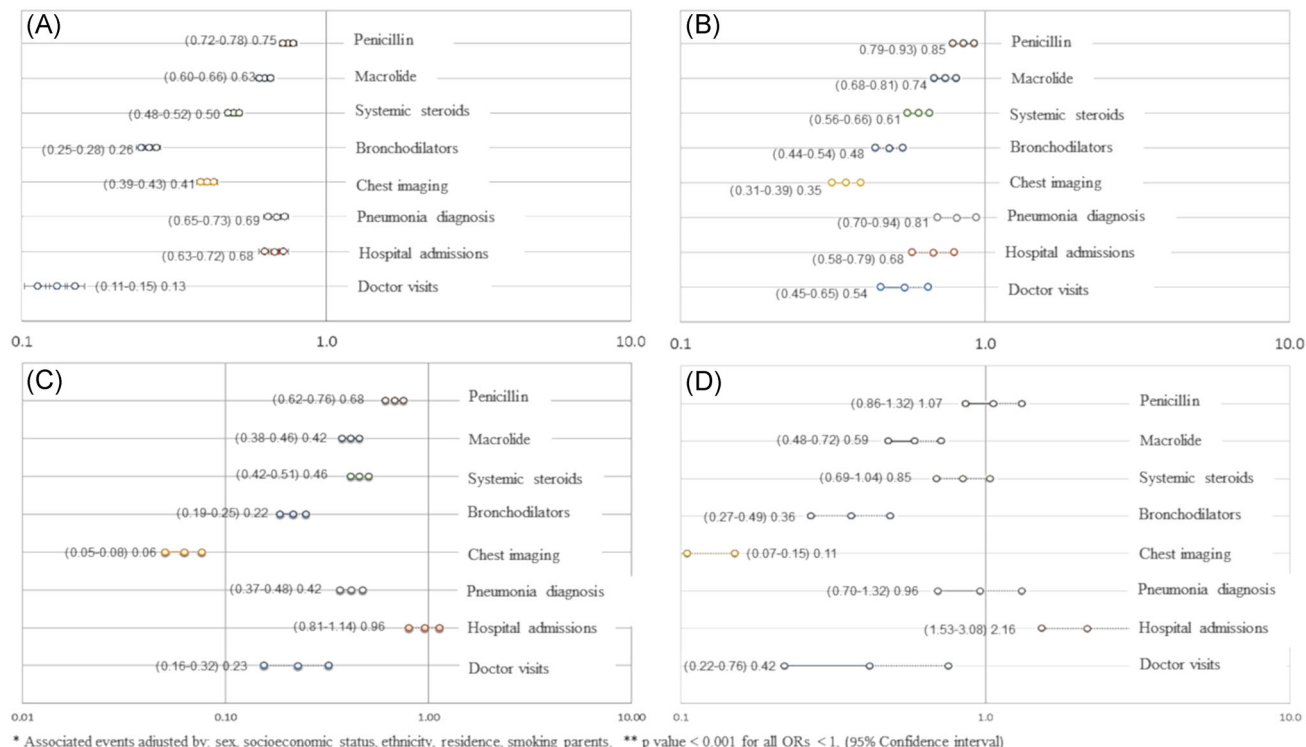


FIGURE 2 Odds ratio for decreased health care and medication usage during controller treatment. A, Three months following initiation of inhaled corticosteroids. B, Three months following initiation of leukotriene receptor antagonists. C, Twelve months following initiation of inhaled corticosteroids. D, Twelve months following initiation of leukotriene receptor antagonists

Three months' ICS or LTRA therapy significantly reduced the mean number of all health care services, pneumonia diagnosis, and medication purchase. Twelve months' of ICS reduced the mean number of all health care services, pneumonia diagnosis, and medication purchase, but not hospital admissions. LTRA significantly reduced the mean number of doctor visits, bronchodilators, and systemic steroids purchase.

4 | DISCUSSION

This study is the largest to date evaluating young infants and toddlers with asthma-like symptoms. The access to such a large medical database provides us with a rich source of information and reveals that the frequency of asthma-like symptoms in infants and toddlers is high. Over a third of all infants fulfilled GINA criteria for asthma-like symptoms,⁶ similar to the Tucson and Bisgaard studies,¹⁶⁻¹⁸ but double that in two recent real-world epidemiological studies.^{19,20} However, only a small minority received controller therapy, even using permissive criteria of 50% of the recommended dose to define controller user.

Our findings shed an important light on the real-world management of these infants and toddlers. The group who received controller therapy was analyzed in depth with regard to health care utilization and revealed that the burden of care is very high. There appears to be an overwhelming overuse of chest X-rays and antibiotics for what are mostly viral-based episodes in this age

group.²¹ Current evidence further suggests that oral steroids are of limited value for the treatment of what is frequently viral wheeze in these young children, especially as outpatients.²² Any subsequent plan to impact these practices would do well to consider what drives health care practices of primary care pediatricians for this population. An interesting study from the Netherlands described physician prescribing behavior as a main determinant of adherence to ICS therapy and that many patients, including those with viral wheeze, receive frequent brief intermittent ICS courses.²³ Our findings of likely overtreatment with antibiotics and oral steroids, suggests that in our population as well, treatment decision by health care providers in this population are not guideline based.

We have shown that controller therapy was associated with a significant reduction in health care utilization, although it remained high. This would likely benefit many of the infants with recurrent asthma-like symptoms who did not receive controller medication in our population, and who indeed fulfill GINA guidelines.¹⁸ By comparison, a recent Belgian study showed 28% controller use in young wheezing infants.²⁴ Most studies, including two meta-analyses,^{25,26} have found that ICS in young children reduce exacerbations, oral steroid, and bronchodilator use. However, these studies were smaller,^{27,28} usually including children over 1 year of age,²⁷⁻³¹ with short follow-up periods.²⁸⁻³² Most did not include children with chronic or recurrent cough,²⁵ although the 2017 GINA guidelines define children with over two recurrent prolonged cough episodes following a viral illness as asthmatic, at least at this stage of life.⁶

Low SES was associated with a higher prevalence of wheezing in infants but controller therapy was less prevalent within the

TABLE 4 Change in mean number of health care services and medications for each patient

A. Three months before and following initiation of controller therapy								
Outcomes	ICS treatment				LTRA treatment			
	Mean		Delta (95% CI)		Mean		Delta (95% CI)	
	3 Mo pre	3 Mo post	*adjusted	P value*	3 Mo pre	3 Mo post	*adjusted	P value*
Doctor visits	3.50	3.08	-0.40 (-0.45-0.36)	<.001	4.02	2.68	-1.31 (-1.40-1.21)	<.001
Hospital admissions	0.13	0.09	-0.04 (-0.05-0.03)	<.001	0.09	0.06	-0.03 (-0.04-0.02)	<.001
Pneumonia diagnosis	0.24	0.17	-0.06 (-0.08-0.05)	<.001	0.13	0.11	-0.03 (-0.05-0.01)	.004
Chest X-rays	0.39	0.20	-0.19 (-0.20-0.18)	<.001	0.35	0.15	-0.20 (-0.22-0.18)	<.001
Bronchodilators	1.41	1.18	-0.23 (-0.25-0.21)	<.001	1.53	1.13	-0.40 (-0.44-0.36)	<.001
Systemic steroids	1.40	1.00	-0.40 (-0.43-0.36)	<.001	1.54	1.05	-0.51 (-0.58-0.44)	<.001
Macrolide	0.63	0.47	-0.16 (-0.18-0.14)	<.001	0.73	0.58	-0.16 (-0.21-0.11)	<.001
Penicillin	1.03	0.91	-0.11 (-0.15-0.08)	<.001	1.27	1.08	-0.19 (-0.25-0.12)	<.001
B. Twelve months before and following initiation of controller therapy								
Outcomes	ICS treatment				LTRA treatment			
	Mean		Delta (95% CI)		Mean		Delta (95% CI)	
	12 Mo pre	12 Mo post	*adjusted	P value	12 Mo pre	12 Mo post	*adjusted	P value
Doctor visits	8.41	5.14	-3.35 (-3.82-2.87)	<.001	8.85	7.58	-0.99 (-1.99-0.07)	.04
Hospital admissions	0.11	0.10	-0.01 (-0.03-0.05)	.68	1.08	1.18	0.82 (0.00-3.54)	.09
Pneumonia diagnosis	0.58	0.24	-0.33 (-0.44-0.22)	<.001	1.96	1.53	-0.52 (-2.08-3.65)	.6
Chest X-rays	0.53	0.04	-0.47 (-0.54-0.40)	<.001	1.42	1.10	-0.68 (-2.22-2.22)	1
Bronchodilators	3.39	1.55	-1.57 (-1.80-1.33)	<.001	3.66	2.70	-1.01 (-1.54-0.63)	<.001
Systemic steroids	2.51	1.22	-1.51 (-1.80-1.22)	<.001	4.04	3.05	-1.19 (-2.61-0.32)	.01
Macrolide	1.35	0.65	-0.61 (-0.79-0.42)	<.001	2.64	2.04	-0.50 (-1.14-0.54)	.48
Penicillin	2.25	1.71	-0.89 (-1.17-0.61)	<.0001	3.46	3.06	-0.50 (-1.37-0.22)	.16

Note: Associated events adjusted by: sex, socioeconomic status, ethnicity, residence, and smoking parents.

Abbreviations: CI, Confidence interval; ICS, Inhaled corticosteroids; LTRA, leukotriene receptor antagonist.

*Linear regression was used for the adjustment of all variables. P value throughout indicates significant differences between pre vs post treatment measured outcomes after adjustment.

Orthodox Jewish and Arab populations who tend to have a lower SES as well as larger families and more crowded living conditions.³³ The Latino studies of wheezing infants found that a low household income per month was associated with a higher prevalence of recurrent wheezing and severity markers^{19,34} whereas others showed only a slight effect of SES on wheezing in young children and no effect in adolescents in Canada.³⁵

Our study included the youngest of infants, and indeed we found that the mean age of onset of asthma-like symptoms was within the first year of age and was lower in those using controller therapy possibly suggesting a more severe phenotype.

Number of hospitalizations did not decrease following prolonged controller therapy and even increased for those on LTRA for 12 months. This is not entirely surprising. Both Calpins' meta-analysis and a Cochrane's analysis could not show benefit with regard to hospital admissions with use of ICS controllers.^{26,36} Presumably our group receiving controller therapy for a year had more severe asthma, and therefore a higher chance of repeated hospitalization.

Indeed, hospitalization of itself is a marker of severe asthma, as shown in a study of severe therapy-resistant asthma³⁷ with a risk of readmissions following lower respiratory infections.³⁸

We found that ICS were more effective than LTRA although both were associated with reduced health care utilization. Indeed, the GINA guidelines recommend ICS as the first line and LTRA as only the second line for controller therapy in young children.⁶ The PREVIA (Prevention of Viral-Induced Asthma) study³⁹ demonstrated that montelukast used daily for 12 months reduced the risk of exacerbation in 2 to 5-year-old children and a retrospective pediatric study found that the risk of emergency department visits, hospitalizations, and oral corticosteroid use was similar with LTRA and ICS as controller.¹³ However, other studies failed to demonstrate the effectiveness of LTRA as a controller in young children.⁴⁰

The number of chest radiographs following controller therapy was markedly reduced, probably associated with the decreased complications of uncontrolled asthma. Chest radiographs constitute an exposure to radiation (80-110 uGy)⁴¹ with associated

risks⁴² and a burden on limited health resources. Similarly, there were less diagnoses of pneumonia following controller therapy which is encouraging, considering the global health burden and mortality due to pneumonia in young children.⁴³ Consistent with this finding, both the rate and absolute number of antibiotic purchases decreased. Penicillin and macrolides are the most prescribed antibiotics for proven or suspected lower respiratory infections in children with asthma-like symptoms with up to 35% treated with antibiotics,⁴⁴ despite the fact that these infections are mostly commonly viral and trigger wheezing in young children.⁴² De Boeck et al found that antibiotics are more commonly dispensed to children who have had an asthma drug dispensed.²⁴

Some of the children requiring repeated courses of bronchodilator and thus considered to require controller therapy, may in fact have been mildly affected despite recurrent episodes, but these could not be differentiated from the others using the database. Nevertheless, considering the high prevalence of recurrent asthma-like symptoms and the significant reduction in health care utilization including doctor visits, chest imaging, bronchodilator, and oral steroids purchase, these findings suggest that the financial burden could be markedly reduced if controller therapy were instituted where appropriate according to asthma guidelines for this age group.

The strengths of this study, beyond the large sample size, are the long period of follow-up and the young age of the patients, as well as the collection of objective data.

As with most real-world database research, ours has several inherent weaknesses, including its retrospective nature, based solely upon electronic medical records, and without the possibility of evaluating the actual consumption of medication. Because a control group is lacking in this kind of study, we cannot eliminate the placebo effect of instituting controller therapy. The most important limitation was our inability to compare the treated and nontreated cohorts with asthma-like symptoms as the large group of untreated children was heterogeneous, differing in demographics and baseline parameters from the treated group. Furthermore, the untreated group could not be categorized by severity levels using the data in the electronic records, so that we could not identify an appropriately matched cohort of untreated children with asthma-like symptoms to compare with the treated group. Other large real-world studies used therapeutic typologies to classify infants into groups of severity based on treatments before the index date: infants with no asthma treatment, infants with reliever therapy alone, and infants already receiving controller therapy.²⁰ Since controller therapy was the intervention in this study, it was statistically incorrect to use it as part of a severity score. We could therefore not exclude the role played by natural history as a bias of pre/post analysis. Many toddlers have decreasing symptoms over time, and medication is started in the period when symptoms are most severe. This was a lesser confounder for the 3 months compared with 12 months comparison period. Seasonality may have played a role in the improvement after 3 months, if respiratory symptoms began in winter and ceased in summer, although we compared the

pre-controller findings to the period from only 1 month after institution of controller therapy. Furthermore, the results over 12 months of treatment eliminate the effect of seasonality. The criterion of "two or more bronchodilator purchases" was used to define recurrent asthma-like symptoms. This was a bias influencing baseline bronchodilator use. However, as an outcome measure, we were interested in the change in bronchodilator use over time, making this bias less relevant. The fact that the ICS group included some infants also receiving LTRA, reduces somewhat the ability to compare the effectiveness of ICS to LTRA. Finally, the prescribing behavior of the physician after starting ICS in an infant may influence consecutive treatment decisions, and might bias the reduction effect of health care utilization.²³

5 | CONCLUSIONS

Asthma-like symptoms are common within the population of Israeli infants and toddlers; however, controller therapy, particularly with inhaled corticosteroids, is used in only a small proportion of these children. We found that health care utilization, and particular doctor visits, is extremely high in this group of children. Physician practices do not appear to follow guidelines with respect to overuse of chest X-rays, oral steroids, and antibiotics, and conversely, likely underutilization of controller therapy. Institution of controller therapy is associated with a reduction in doctor visits and other respiratory-related health care utilization. Our findings strengthen the recommendation of the current GINA guidelines which suggest controller therapy with ICS for infants and toddlers with asthma.

ACKNOWLEDGEMENT

The study was supported by Clalit Research Institute and Clalit Health Services.

CONFLICT OF INTERESTS

The authors have no conflicts of interest relevant to this article to disclose.

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REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332(3):133-138.
2. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax*. 2008;63(11):974-980.

3. Bloomberg GR. Recurrent wheezing illness in preschool-aged children: Assessment and management in primary care practice. *Postgrad Med*. 2009;121:48-55.
4. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--United States, 1980-1999. *MMWR Surveill Summ*. 2002;51(1):1-13.
5. Bacharier LB, Boner a, Carlsen K-H, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy*. 2008;63(1):5-34.
6. Page PM, Broek JL, Bousquet J, et al. Global strategy for asthma management and prevention. *Glob Initiat Asthma*. 2017;126(3):1-159. <http://ginasthma.org/2017-gina-report-global-strat>
7. Guilbert TW, Morgan WJ, Krawiec M, et al. The prevention of early asthma in kids study: design, rationale and methods for the childhood asthma research and education network. *Control Clin Trials*. 2004;25:286-310.
8. Bisgaard H, Gillies J, Groenewald M, Maden C, Groenewald M, Maden C on behalf of an ISG. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med*. 1999;160:126-131.
9. Pedersen S. Do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med*. 2001;164(4):521-535.
10. Kelly HW, VanNatta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood asthma management program (CAMP) study. *Pediatrics*. 2008;122(1):e53-e61.
11. Hilton R, Zheng Y, Fitzpatrick A, Serban N. Uncovering longitudinal health care behaviors for millions of medicaid enrollees: a multistate comparison of pediatric asthma utilization. *Med Decis Mak*. 2017;38(1):107-119.
12. Jentzsch NS, Camargos P, Sarinho ESC, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. *Respir Med*. 2012;106(3):338-343.
13. Wu AC, Li L, Fung V, et al. Use of leukotriene receptor antagonists are associated with a similar risk of asthma exacerbations as inhaled corticosteroids. *J Allergy Clin Immunol Pract*. 2014;2(5):607-613.
14. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162(4 1):1403-1406.
15. Castro-Rodriguez JA. The asthma predictive index: a very useful tool for predicting asthma in young children. *J Allergy Clin Immunol*. 2010;126(2):212-216.
16. Taussig LM, Wright a L, Morgan WJ, Harrison HR, Ray CG. The Tucson children's respiratory study. I. Design and implementation of a prospective study of acute and chronic respiratory illness in children. *Am J Epidemiol*. 1989;129(6):1219-1231.
17. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol*. 2003;111(4):661-675.
18. Bisgaard H, Szefer S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol*. 2007;42(8):723-728.
19. Mallol J, Solé D, Garcia-marcos L, et al. Prevalence, severity, and treatment of recurrent wheezing during the first year of life: a cross-sectional study of 12,405 Latin American infants. *Allergy Asthma Immunol Res*. 2016;8(1):22-31.
20. Belhassen M, dePouvourville G, Laforest L, et al. Effectiveness of Montelukast on asthma control in infants: methodology of a French claims data study. *BMC Pulm Med*. 2015;15(1):51.
21. Mummidi PS, Tripathy R, Dwibedi B, Mahapatra A, Baraha S. Viral aetiology of wheezing in children under five. *Indian J Med Res*. 2017;145(FEBRUARY):189-193.
22. Ommen A, Lambert PCGJ. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial. *Lancet*. 2003;362(9394):1433-1433.
23. Klok T, Kaptein AA, Duiverman E, Oldenhof FS, Brand PLP. General practitioners' prescribing behaviour as a determinant of poor persistence with inhaled corticosteroids in children with respiratory symptoms: mixed methods study. *BMJ Open*. 2013;3(4):e002310.
24. DeBoeck K, Vermeulen F, Meyts I, Hutsebaut L, Franckaert D, Proesmans M. Coprescription of antibiotics and asthma drugs in children. *Pediatrics*. 2011;127(6):1022-1026.
25. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics*. 2009;123(3):e519-e525.
26. Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. *J Allergy Clin Immunol*. 1997;100(4):452-457.
27. Qaqundah PY, Sugerman RW, Ceruti E, et al. Efficacy and safety of fluticasone propionate hydrofluoroalkane inhalation aerosol in pre-school-age children with asthma: a randomized, double-blind, placebo-controlled study. *J Pediatr*. 2006;149:663-670.
28. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med*. 2000;162(4 1):1500-1506.
29. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med*. 2006;354(19):1985-1997.
30. Carlsen KC, Stick S, Kamin W, Cirule I, Hughes S, Wixon C. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med*. 2005;99:1393-1402.
31. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol*. 2001;108:540-546.
32. Wasserman RL, Baker JW, Kim KT, et al. Efficacy and safety of inhaled fluticasone propionate chlorofluorocarbon in 2- to 4-year-old patients with asthma: results of a double-blind, placebo-controlled study. *Ann Allergy, Asthma Immunol*. 2006;96:808-818.
33. Economic Characteristics and Housing Density. *The Central Bureau of Statistics*. 2016;(1):2017. http://www.cbs.gov.il/reader/?Mlval=cw_usr_view_SHTML&ID=406
34. Mallol J, Andrade R, Auger F, Rodríguez J, Alvarado R, Figueroa L. Wheezing during the first year of life in infants from low-income population: a descriptive study. *Allergol Immunopathol (Madr)*. 2005;33(5):257-263.
35. Blais L, Beauchesne MF, Lévesque S. Socioeconomic status and medication prescription patterns in pediatric asthma in Canada. *J Adolesc Heal*. 2006;38(5):607.e9-607.e16.
36. Chong J, Haran C, Chauhan BF, Asher I. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. [Review]. *Cochrane Database Syst Rev*. 2015;7(2):011032.
37. Pitrez PM, deSouza RG, Roncada C, et al. Impact of omalizumab in children from a middle-income country with severe therapy-resistant asthma: a real-life study. *Pediatr Pulmonol*. 2017;52(11):1408-1413.
38. Nakamura M, Zaslavsky A, Toomey SL, et al. Pediatric readmissions after hospitalizations for lower respiratory infections. *Pediatrics*. 2017;140(2):e20160938.
39. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med*. 2005;171(4):315-322.
40. Kooi EMW, Schokker S, Marike Boezen H, et al. Fluticasone or montelukast for preschool children with asthma-like symptoms: randomized controlled trial. *Pulm Pharmacol Ther*. 2008;21(5):798-804.
41. Hart D, Hillier MC, Wall BF. Doses to patients from medical X-ray examinations in the UK - 2000 review. *Nrpb*. 2002;(May 2002):1-66.

42. Brand PLP, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: An evidence-based approach. *Eur Respir J*. 2008;32(4):1096-1110.
43. Fischer Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013;381(9875):1405-1416.
44. Jansen AG, Sanders EA, Schilder AG, et al. Primary care management of respiratory tract infections in Dutch preschool children. *ScandJ-PrimHealth Care*. 2006;24(4):231-236.

How to cite this article: Levine H, Leventer-Roberts M, Hoshen M, Mei-Zahav M, Balicer R, Blau H. Healthcare utilization in infants and toddlers with asthma-like symptoms. *Pediatric Pulmonology*. 2019;1-11.
<https://doi.org/10.1002/ppul.24429>