

Risk Factors for Severe Bronchiolitis in Children admitted at Birat Medical College Teaching Hospital

Yadav S, Yadav R, Mahat RK, Rimal H

Department of Pediatrics,

Birat Medical College and Teaching Hospital,

Budhiganga-2, Tankisinuwari, Morang, Nepal.

Corresponding Author

Satish Yadav

Department of Pediatrics,

Birat Medical College and Teaching Hospital,

Budhiganga-2, Tankisinuwari, Morang, Nepal.

E-mail: satishdryadav@gmail.com

Citation

Yadav S, Yadav R, Mahat RK, Rimal H. Risk Factors for Severe Bronchiolitis in Children admitted at Birat Medical College Teaching Hospital. **Online First.**

ABSTRACT

Background

Bronchiolitis is the most common cause of hospitalization in infants under the age of 2 years. There are various risk factors associated with severe disease. Therefore, identifying risk factors of severe bronchiolitis and acting promptly is foremost to avoid its adverse outcome.

Objective

To find out the socio-demographic, clinical profile and risk factors associated with severe bronchiolitis.

Method

This was hospital based cross-sectional study of data of children between 3 months to 2 years admitted in the Department of Pediatrics with a clinical diagnosis of bronchiolitis from September 2023 to May 2024. Various factors were recorded to identify risk factors for severe bronchiolitis.

Result

Ninety children were included in the study with a majority of age group 3 to 12 months (76%) and male to female ratio of 1.8. The most common symptoms were cough (85%), fever (76%), blocked nose (56%) and difficulty in breathing (35%). On applying bivariate analysis, age group, lack of exclusive breast feeding, having siblings and low maternal literacy were significant risk factors whereas on applying multivariate analysis, were found significant associations between having siblings (Adjusted Odd Ratio=5.555, 95% Confidence Interval=1.332-23.169, p value= 0.019) and low maternal literacy (Adjusted Odd Ratio =0.233, 95% Confidence Interval =0.063-0.859, p value= 0.002) for severe bronchiolitis.

Conclusion

In our study, cough and fever were the most common symptoms of bronchiolitis. Having siblings and low maternal literacy were the significant risk factors for severe bronchiolitis.

KEY WORDS

Bronchiolitis, Children, Risk factors, Severe disease, Siblings

INTRODUCTION

Bronchiolitis is one of the most common condition for hospitalization in infants and young children worldwide.¹ An estimated 150 million new cases are reported worldwide annually among them 2% to 3% require hospitalization.² Ninety-five percent of all cases occur in developing countries. Globally, it is the most prevalent cause of hospitalization in infants resulting in a significant morbidity and mortality.^{3,4}

The most common cause of bronchiolitis is Respiratory Syncytial Virus.⁵ It is the acute inflammation of the bronchioles which causes edema, increased mucus production, necrosis of epithelial cells and inadequate oxygenation of tissues.⁶ The disease has different clinical courses, whose symptoms can range from mild to severe and sometimes leading to respiratory failure and death. This is due to their smaller airway which gets easily obstructed and their decreased ability to clear secretions. There are various risk factors associated with severe bronchiolitis in young children. Severe cases occur more frequently in males and younger infants.⁷ Moreover, prematurity, low birth weight and delivery by caesarean section were the factors that increase the risk of severe bronchiolitis.^{6,8} Factors such as cigarette smoke, exposure to cooking fuel and having siblings can also contribute to the severity of bronchiolitis.^{9,10} Other associated risk factors include the lack of exclusive breastfeeding for six months, malnutrition and a family history of asthma.¹¹

However, there are only a paucity of literature available on risk factors for the development of severe bronchiolitis in Nepal. Hence, the present study was undertaken to identify risk factors for severe disease in our region will help to decrease the cost of healthcare as well as mortality. This study aimed to identify various risk factors associated with severe bronchiolitis such as age, gender, residency, prematurity, mode of delivery, exposure to cigarette smoke, cooking fuel, exclusive breastfeeding, nutritional status, having siblings, maternal literacy and recent family history of acute respiratory infection (ARI).

METHODS

This was a hospital based cross-sectional study held at Birat Medical College and Teaching Hospital, Budhiganga-2, Tankisinuwari, Morang, Nepal from September 2023 to May 2024. Subjects were sampled by non-probability consecutive sampling technique who met the inclusion criteria. We used $n = \frac{4 \times P \times Q}{L^2}$ formula to calculate sample size (n-sample size, P-approximate prevalence, Q = 1-P, L = Allowable error (required precision). Available incidence is 7% of children need admission due to bronchiolitis.¹²

$$P = \frac{7}{100} = 0.07$$

$$Q = 1 - P = 1 - 0.07 = 0.93$$

Allowable error 6%

$$L = \frac{6}{100} = 0.06$$

At 95% confidence level

For 95% confidence level, Z = 1.96, and therefore 4; which is approximate square of "Z" is taken

$$n = \frac{4 \times 0.07 \times 0.93}{(0.06)^2} = 72$$

So, the calculated sample size was 72. However, we took all cases during study period. Written consent from parents were taken before including in the study. This study was start after approval by the Research Ethic Committee of Birat Medical College [IRC-PA-332/2023]. All cases between 3 months to 24 months of age with a diagnosis of bronchiolitis admitted under the pediatric department were included in the study. Cases with heart disease, asthma, second episodes of wheeze, immunodeficiency, congenital anomalies and refusal for consent were excluded.

The various risk factors which were recorded which includes age, gender, residency (rural/urban), term\preterm, chest X-ray (hyperinflated/normal), exclusive breastfeeding, exposure to cigarette smoking, mode of delivery, having siblings, maternal education (literate/illiterate), firewood exposure, malnutrition and family history of respiratory tract infection in last 2 weeks.

The diagnostic criteria of the American Academy of Pediatrics (AAP) in 2014 was followed.¹³ The criteria for diagnosis is follows: (i) Symptoms of inflammation of the upper respiratory tract: fever, cough, sneezing, and rhinorrhea (ii) Progressing to tachypnea, chest indentation, or intercostal muscle pull within 48 to 72 hours. Signs of air trapping in clinical examination or chest X-ray (iii) Wheezing for the first time (iv) Rhonchi, or crackles in chest examination. The severity of bronchiolitis will be based on Wood-Downes Clinical Scoring System Modified by Ferres (Table 1).¹⁴

Table 1. Wood-Downes Clinical Scoring System Modified by Ferres¹⁴

Variables	0	1	2	3
Wheezing	None	End expiration	Entire expiratory phase	Inspiration and expiration
Retractions	None	Subcostal or lower intercostal	1 + supra-clavicular + nasal flaring	2 + supra-sternal + lower intercostal
Respiratory rate (breaths / Min)	< 30	31-45	46-60	> 60
Heart rate (beats/min)	< 120	> 120		
Inspiratory breath sounds	Normal	Regular, symmetrical	Markedly silent, symmetrical	Silent thorax, no wheezing
Cyanosis	Not present	Present		
A score of bronchiolitis;	1-3 points (mild)	4-7 points (moderate)	8-14 points (severe bronchiolitis)	

Age was taken in complete months and further divided in 3 to 12 months and 12 to 24 months. Malnutrition was defined by the World Health Organization (WHO) for severe and moderate acute malnutrition as (I) weight for height/length $<-3Z$ score and -2 to $-3Z$, respectively; (II) presence of visible severe wasting; (III) nutritional edema; (IV).¹⁵ The mother who can write and read were categorized as a literate mother. Breastfeeding exclusively till 6 months then continued feeding till age 2 years was labeled as appropriate breast feeding.

Statistical program for Social Sciences (SPSS) 26.0 version was used for all statistical analysis. Data was summarized by using frequency and percentage for qualitative variables. A bivariate analysis by chi squared statistic was carried out to determine the association between various risk factors and severity of bronchiolitis. Variables which has $p < 0.05$ were subsequently put on stepwise multiple logistic regression model to determine the significant independent risk factor of severe disease.

RESULTS

There were 90 children from 3 to 24 months old with bronchiolitis admitted to Birat Medical Teaching Hospital, Nepal over the period from September 2023 to May 2024 were included in this study. Among them, 58 (64%) males and 48 (53%) from urban areas. In our study, the majority of children were from 3 to 12 months 69 (76%) of age group. Regarding the severity of bronchiolitis, 63 (70%) of children suffered from mild-moderate bronchiolitis, and 27 (30%) from severe bronchiolitis (Table 2). The common clinical symptoms are illustrated in table 3. In children with bronchiolitis, we investigated a variety of potential risk factors related to severe bronchiolitis. In bivariate analysis, the significant risk factors for severe bronchiolitis were age group, lack of exclusive breastfeeding, having siblings and maternal education status, whereas on multivariate analysis, having siblings and low maternal education were only independent significant risk factors for severe bronchiolitis (Table 4).

DISCUSSION

In this study, various risk factors were identified for severe bronchiolitis. Among them, age group, lack of exclusive breastfeeding, having siblings and an illiterate mother were identified as risk factors for severe disease on bivariate analysis, whereas having siblings and an illiterate mother were the only independent risk factors found on multivariate analysis.

Bronchiolitis is a common respiratory illness in children of less than 2 years and 80% of hospitalizations occur in the first year.¹⁶ A study by Hall et al. also found a significant association between the age of less than 6 months and a higher risk of hospitalization and severe bronchiolitis.¹⁷ This

Table 2. Socio-Demographic profile of children with bronchiolitis

Variable	Number of patients (n)	Percentage (%)
Gender		
Male	32	35.6
Female	58	64.4
Age group		
3 to 12 months	69	76.7
12 to 24 months	21	23.3
Residency		
Urban	48	53.3
Rural	42	46.7
Severity of bronchiolitis		
Mild to Moderate	63	70.0
Severe	27	30.0

Table 3. Clinical features of children with bronchiolitis

Clinical features	Number of patients (%)
Cough	77 (85.6)
Fever	69 (76.7)
Nasal blockage	51 (56.7)
Difficulty in breathing	32 (35.6)
Feeding problem	18 (20.0)

is probably secondary to reduced immunity in early infancy toward viral infections and due to their smaller airway which gets easily obstructed and their decreased ability to clear secretions.¹⁸ In this study, most of the children were from the age group of 3 months to 1 year (76.7%). Our study showed significant association between age group and severe disease in bivariate analysis but unexpectedly insignificant in multivariate analysis (Adj. OR=3.612, 95% CI 0.901-14.479, p-value 0.011).

Breastfeeding helps to build a strong immune system in infants which gives protection against serious infections.¹⁹ WHO and UNICEF recommend breastfeeding to be initiated within the first hour of birth and to continue exclusively for the first 6 months.²⁰ The protective effect of breastfeeding observed may be due to the fact that breast milk contains substances that may have biological effects that can promote lung growth and improve lung function.²¹ Breast milk also contains numerous anti-inflammatory and immunological agents.²² Our study showed that exclusive breastfeeding had significant association on bivariate analysis and no significant association on multivariate analysis. Contrarily, other studies showed that breastfeeding reduces the risk of severe bronchiolitis as well as hospitalization in intensive care units.²³ However, similar to our study, other studies also failed to find any association between breastfeeding and severity of bronchiolitis.^{24,25}

Table 4. Risk factors associated with severe bronchiolitis

Characteristics	Categories	Severity		p-value	COR	Adj. OR	95% CI	
		Mild to Moderate	Severe				Lower	Upper
Age group (months)	3 – 12	53 (76.8)	16 (23.2)	0.011	Reference			
	12 – 24	10 (47.6)	11 (52.4)		3.644	3.612	0.901	14.479
Gender	Female	24 (75.0)	8 (25.0)	0.442	Reference			
	Male	39 (67.2)	19 (32.8)		1.462			
Residency	Urban	34 (70.8)	14 (29.2)	0.854	Reference			
	Rural	29 (69.0)	13 (31.0)		1.089			
Chest X-Ray	Normal	34 (73.9)	12 (26.1)	0.408	Reference			
	Abnormal	29 (65.9)	15 (34.1)		1.466			
Nutritional status	No	52 (71.2)	21 (28.8)	0.597	Reference			
	Yes	11 (64.7)	6 (35.3)		1.351			
Prematurity	No	59 (72.0)	23 (28.0)	0.196	Reference			
	Yes	4 (50.0)	4 (50.0)		2.565	6.418	0.94	43.799
Exclusive Breast Feeding	No	15 (53.6)	13 (46.4)	0.022	Reference			
	Yes	48 (77.4)	14 (22.6)		0.337	0.361	0.106	1.231
Family history of Smoking	No	45 (75.0)	15 (25.0)	0.143	Reference			
	Yes	18 (60.0)	12 (40.0)		2.000	1.797	0.514	6.277
Having Sibling	No	28 (84.8)	5 (15.2)	0.019	Reference			
	Yes	35 (61.4)	22 (38.6)		3.520	5.555	1.332	23.169
Number of sibling (n=57)	1	22 (73.3)	8 (26.7)	0.051	Reference			
	2	13 (48.1)	14 (51.9)		2.962			
Sibling going to school (n=57)	No	17 (68.0)	8 (32.0)	0.366	Reference			
	Yes	18 (56.2)	14 (43.8)		1.653			
Mode of Delivery	Normal	36 (75.0)	12 (25.0)	0.268	Reference			
	CS	27 (64.3)	15 (35.7)		1.667			
Maternal Education	Illiterate	9 (42.9)	12 (57.1)	0.002	Reference			
	Literate	54 (78.3)	15 (21.7)		0.208	0.233	0.063	0.859
Cooking fuel	LPG	38 (74.5)	13 (25.5)	0.286	Reference			
	Wood	25 (64.1)	14 (35.9)		1.637			
Family History of respiratory tract infection in last 2 weeks	No	47 (75.8)	15 (24.2)	0.074	Reference			
	Yes	16 (57.1)	12 (42.9)		2.350	4.11	1.074	15.732
Total		63 (70.0)	27 (30.0)					

Infants with older siblings have an increased risk of acquiring viral infections and are more likely to be admitted to hospital with bronchiolitis.²⁶ Older siblings who go to school are a major source for transmitting viral infections.^{27,28} This could be explained by the greater likelihood for viral exposure and infection among infants with a sibling.²⁹ In our study, we found that children who have sibling appear to be important risk factors for severe bronchiolitis. However, we didn't find any association between number of siblings and school going older siblings with severity of bronchiolitis. Similar finding was found by Canadian PICNIC study which revealed that the presence of preschool-aged siblings was significantly and independently associated with an increased risk for hospitalization, and a weaker association was found with the presence of school-aged siblings.³⁰ In contrast, the Spanish FLIP study revealed that only school-aged siblings was risk factors significantly associated with hospitalization.³¹

A study by Nguyen et al. showed that maternal education was as a significant risk factor of severe bronchiolitis.⁸ Similarly, another study also showed low maternal educational level as a risk factor for hospitalization for bronchiolitis.³² Similarly, our study also revealed that children with literate mothers as a protective factor for acquiring severe disease. The protective effect of parental education against severe disease may be due to more awareness about the infection, its care and early seeking for medical care.

The limitation of the study is the data is that we excluded infants under 3 months of age. The sample size is small and was carried out in only one referral center. We need large scale study to understand the factors associated with severe bronchiolitis in Eastern part of Nepal. We suggest that future work include samples from a greater geographic area or be expanded to a multi-center analysis.

CONCLUSION

There is no specific treatment for bronchiolitis. It is usually supportive. Identifying risk factors for severe disease will lower the cost as well as avoid mortality. This study identified having siblings and lower maternal education as the risk factors for severe bronchiolitis. These findings provided valuable information to identify factors associated with severe disease in our region. However, it is important

to identify other considerable risk factors in our region by conducting multi-center studies.

ACKNOWLEDGEMENTS

I would also like to thank Dharni Dhar Baral for his help with data analysis. We extend our heartfelt gratitude to the participants and faculty of the department of pediatrics who helped me to conduct this study.

REFERENCES

- Baldassarre ME, Loconsole D, Centrone F, Caselli D, Martire B, Quartulli L, et al. Hospitalization for bronchiolitis in children aged ≤ 1 year, Southern Italy, year 2021: need for new preventive strategies? *Ital J Pediatr*. 2023 Jun 6;49(1):66.
- Tian J, Wang XY, Zhang LL, Liu MJ, Ai JH, Feng GS, et al. Clinical epidemiology and disease burden of bronchiolitis in hospitalized children in China: a national cross-sectional study. *World J Pediatr*. 2023 Sep;19(9):851-63.
- House SA, Ralston SL. Diagnosis, prevention, and management of bronchiolitis in children: review of current controversies. *Minerva Pediatr*. 2017 Apr;69(2):141-155. doi: 10.23736/S0026-4946.16.04865-9. PMID: 28178775.
- Ursin RL, Klein SL. Sex Differences in Respiratory Viral Pathogenesis and Treatments. *Annu Rev Virol*. 2021 Sep 29;8(1):393-414. doi: 10.1146/annurev-virology-091919-092720. Epub 2021 Jun 3. PMID: 34081540.
- Leader S, Kohlhasse K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003 Nov;143(5 Suppl):S127-32. doi: 10.1067/s0022-3476(03)00510-9. PMID: 14615711.
- Robledo-Aceves M, Moreno-Peregrina MJ, Velarde-Rivera F, Ascencio-Esparza E, Preciado-Figueroa FM, Caniza MA, et al. Risk factors for severe bronchiolitis caused by respiratory virus infections among Mexican children in an emergency department. *Medicine (Baltimore)*. 2018 Mar;97(9):e0057. doi: 10.1097/MD.00000000000010057. PMID: 29489664; PMCID: PMC5851717.
- Bradley JP, Bacharier LB, Bonfiglio J, Schechtman KB, Strunk R, Storch G, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics*. 2005 Jan;115(1):e7-14. doi: 10.1542/peds.2004-0059. PMID: 15629968.
- Nguyen SN, Nguyen TNT, Vu LT, Nguyen TD. Clinical Epidemiological Characteristics and Risk Factors for Severe Bronchiolitis Caused by Respiratory Syncytial Virus in Vietnamese Children. *Int J Pediatr*. 2021 Nov 15;2021:9704666. doi: 10.1155/2021/9704666. PMID: 34819958; PMCID: PMC8608547.
- Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. *Respir Res*. 2011 Jan 10;12(1):5. doi: 10.1186/1465-9921-12-5. PMID: 21219618; PMCID: PMC3022703.
- Nenna R, Cutrera R, Frassanito A, Alessandrini C, Nicolai A, Cangiano G, et al. Modifiable risk factors associated with bronchiolitis. *Ther Adv Respir Dis*. 2017 Oct;11(10):393-401. doi: 10.1177/1753465817725722. Epub 2017 Aug 16. PMID: 28812472; PMCID: PMC5933664.
- Kulhalli P, Dakshayini JN, Ratageri VH, Shivanand I, Wari PK. Risk factors for bronchiolitis. *J Pediatr Crit Care*. 2020;7:79-83.
- Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H; WHO Child Health Epidemiology Reference Group. Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bull World Health Organ*. 2004 Dec;82(12):895-903. Epub 2005 Jan 5. PMID: 15654403; PMCID: PMC2623105.
- Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. American Academy of Pediatrics; Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014 Nov;134(5):e1474-502. doi: 10.1542/peds.2014-2742. Erratum in: *Pediatrics*. 2015 Oct;136(4):782. doi: 10.1542/peds.2015-2862. PMID: 25349312.
- Ferrés Mataró J, Mangues Bafalluy MA, Farré Riba R, Juliá Bragues A, Bonal de Falgas J. Adrenalina subcutánea versus salbutamol inhalado en el tratamiento de la crisis asmática infantil [Subcutaneous adrenaline versus inhaled salbutamol in the treatment of childhood asthmatic crisis]. *An Esp Pediatr*. 1987 Jul;27(1):37-40. Spanish. PMID: 3662253.
- World Bank's World Development Indicators: Overcrowded Homes. 20 Populations living in the most overcrowded conditions 2005, Produced by the SASI group (Sheffield) and Mark Newman (Michigan): Map 192
- Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. *J Pediatr*. 1981 May;98(5):708-15.
- Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360:588-98
- Papenburg J, Hamelin MÈ, Ouhoumane N, Carbonneau J, Ouakki M, Raymond F, et al. Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children. *J Infect Dis*. 2012;206:178-89.
- Scrimshaw NS. Book Review: Evidence on the Long-Term Effects of Breastfeeding. *Food and Nutrition Bulletin*. 2008 Mar;29(1):76-6.
- Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016 Jan 30;387(10017):475-90.
- Dogaru CM, Strippoli MP, Spycher BD, Frey U, Beardsmore CS, Silverman M, et al. Breastfeeding and lung function at school age: does maternal asthma modify the effect? *Am J Respir Crit Care Med*. 2012 Apr 15;185(8):874-80.
- Pabst HF, Spady DW, Pilarski LM, Carson MM, Beeler JA, Krezolek MP. Differential modulation of the immune response by breast- or formula-feeding of infants. *Acta Paediatr*. 1997 Dec;86(12):1291-7.
- Midulla F, Scagnolari C, Bonci E, Pierangeli A, Antonelli G, De Angelis D, et al. Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. *Arch Dis Child*. 2010 Jan;95(1):35-41.

24. Leung HW, Hung LL, Chan AL, Mou CH. Long-Term Use of Antihypertensive Agents and Risk of Breast Cancer: A Population-Based Case-Control Study. *Cardiol Ther*. 2015 Jun;4(1):65-76.
25. Nenna R, Cutrera R, Frassanito A, Alessandrini C, Nicolai A, Cangiano G, et al. Modifiable risk factors associated with bronchiolitis. *Thorax*. 2017 Oct;72(10):393-401.
26. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiological features of bronchiolitis in a population-based cohort. *Pediatrics*. 2008 Dec;122(6):1196-203.
27. Pérez-Yarza EG, Moreno-Galdó A, Ramilo O, Rubí T, Escribano A, Torres A, et al. Risk factors for bronchiolitis, recurrent wheezing, and related hospitalization in preterm infants during the first year of life. *Pediatr Allergy Immunol*. 2015 Dec;26(8):797-804. doi: 10.1111/pai.12414. Epub 2015 Jul 1. PMID: 26031206.
28. Carroll KN, Gebretsadik T, Griffin MR, Wu P, Dupont WD, Mitchell EF, et al. Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state health care insurance plan. *Pediatrics*. 2008 Jul;122(1):58-64.
29. Law BJ, Langley JM, Allen U, Paes B, Lee DS, Mitchell I, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J*. 2004 Sep;23(9):806-14.
30. Figueras-Aloy J, Carbonell-Estrany X, Quero J; IRIS Study Group. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33-35 weeks in Spain. *Pediatr Infect Dis J*. 2004 Sep;23(9):815-20.
31. Pezzotti P, Mantovani J, Benincori N, Mucchino E, Di Lallo D. Incidence and risk factors of hospitalization for bronchiolitis in preterm children: a retrospective longitudinal study in Italy. *BMC Pediatr*. 2009 Sep 10;9:56.