Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Clinical Virology 98 (2018) 33–36

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Short communication

Respiratory syncytial virus in Brazilian infants – Ten years, two cohorts

Elinara Wollmeister[a], Alfonso Eduardo Alvarez[a,b], Juliana Cristina Santiago Bastos[c], Fernando Augusto Lima Marson[a,b,d], José Dirceu Ribeiro[a,b], Emílio Carlos Elias Baracat[a], Clarice Weis Arns[c], Adriana Gut Lopes Riccetto[a,*]

[a] Department of Pediatrics, Faculty of Medical Sciences, University of Campinas – Unicamp, São Paulo, Brazil
[b] Center for Research in Pediatrics (CIPED), Department of Pediatrics, Faculty of Medical Sciences, University of Campinas – Unicamp, São Paulo, Brazil
[c] Department of Genetics, Evolution and Bioagents, Biology Institute, University of Campinas – Unicamp, São Paulo, Brazil
[d] Department of Medical Genetics, Faculty of Medical Sciences, University of Campinas – Unicamp, São Paulo, Brazil

ARTICLE INFO

Keywords:
Acute viral bronchiolitis
Clinical data
Epidemiologic data
Polymerase chain reaction
Respiratory syncytial virus
Respiratory viruses

ABSTRACT

Background: Each year, a considerable amount of children will experience at least one episode of acute viral bronchiolitis (AVB) during their first year of life. About 10% of them will be hospitalized, with significant physical and economic burdens.
Objectives: To compare two cohorts of infants with AVB, from same region, in a ten-year interval, regarding epidemiologic factors and viral etiology.
Study design: Cohorts: 142 (2004) and 172 (2014) infants at ages zero to 12 months; clinical diagnosis of AVB; medical care in hospital and genetic screening of nasopharyngeal secretion for respiratory viruses.
Results: The comparative analysis showed a difference in the percentage of respiratory syncytial virus (RSV) positive patients [2004 (33.1%); 2014 (70.3%)] ($p < 0.01$). No differences were noted regarding gender, breastfeeding, tobacco exposure, crowding and maternal education. There was a difference as to the month of incidence (seasonality) of AVB (higher in April 2014). There was a higher age at attendance in the first cohort, and lower birth weight and gestational age ratios in the second cohort ($p < 0.05$). There were no differences in hospitalization time, need of mechanical ventilation and number of deaths, however a difference regarding co-morbidities was noted (higher in 2004) ($p < 0.001$).
Conclusion: None of the analyzed variables had an impact on severity features. Virology and immunology must be considered in this kind of situation, by studying genetic variants and the maturation of the immune system in AVB by RSV or other viruses.

1. Background

Acute Viral Bronchiolitis (AVB) is the most common cause of hospitalization among infants during the first 12 months of life [1]. A variety of viral etiologies are known to cause AVB, particularly the respiratory syncytial virus (RSV) [2]. The RSV virus has two subtypes, A and B, which occur in different frequencies and combinations each year [3,4]. About 10% of the AVB cases demand hospitalization; mortality rates are 1% or less, mainly in cases with associated co-morbidities [5]. An effective vaccine is not available; current treatment is only supportive; preventive measures are limited to very expensive monoclonal antibodies [6]. AVB seems to be correlated with seasonality, gender, gestational birth age, birth weight, breastfeeding, tobacco exposure, crowding, maternal education and viral etiology [7–10]. In this study, epidemiologic risk factors, clinical features and viral identification in nasopharyngeal secretion by polymerase chain reaction (PCR) were evaluated and compared in two cohorts (2004 [11] and 2014) with 314 infants with AVB.

2. Study design

Descriptive study with a comparison of two cohorts; sample was composed of infants under 12 months of age (for effect of comparison between two cohorts) with AVB and that demanded hospitalization. Patients were attended in a metropolitan region, in public and private hospitals, in a seasonal AVB period for the region (April to September).

* Corresponding author at: Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas. Rua Tessália Vieira de Camargo, 126, CIPED sala 14, Cidade Universitária "Zeferino Vaz", CEP: 13083-887, Campinas, São Paulo, Brazil.
E-mail addresses: elinaraw@gmail.com (E. Wollmeister), alfonso@imunevida.com.br (A.E. Alvarez), jusantiago_farmacia@yahoo.com.br (J.C.S. Bastos), fernandolimamarson@hotmail.com (F.A.L. Marson), jdirceuribeiro@gmail.com (J.D. Ribeiro), ebaracat@fcm.unicamp.br (E.C.E. Baracat), arns@unicamp.br (C.W. Arns), aglriccetto@gmail.com (A.G.L. Riccetto).

https://doi.org/10.1016/j.jcv.2017.12.002
Received 24 August 2017; Received in revised form 28 November 2017; Accepted 4 December 2017

Table 1
Epidemiological and clinical data in 2004 and 2014 cohorts of infants with acute viral bronchiolitis.

Feature	Group	2004 (n = 142)	2014 (n = 172)	Total (n = 314)	p-value	Odds ratio	95%CI
Seasonality	April	27	53	80	**0.007**[*]	**0.528**	**0.298** to **0.922**
	May	39	55	94		0.599	0.340 to 1.047
	June	35	35	70		0.709	0.344 to 1.454
	July	16	19	35		0.342	0.111 to 1.006
	August	19	9	28		0.361	0.007 to 3.734
	September	6	1	7		7.504	0.894 to 349
Sex	Female	56	70	116	0.908[*]	0.949	0.587 to 1.531
	Male	86	102	188		Reference	–
Birth weight	< 3000 g	23	71	94	< **0.001**[#]	**0.276**	**0.153** to **0.485**
	> 3000 g	119	101	220		Reference	–
Age at attendance	Months	4.47 ± 2.99	3.76 ± 2.85	4.08 ± 2.94	**0.019**[¥]		
		3.5 (1–11)	3 (0–11)	3 (0–11)			
Gestational age	< 37 weeks	14	40	54	**0.002**[#]	**0.361**	**0.187** to **0.695**
	≥ 37 weeks	128	132	260		Reference	–
Breastfeeding	< 1 month	50	50	100	0.397[#]	1.304	0.787 to 2.161
	≥ 1 month	92	120	212		Reference	–
Tobacco exposure	Yes	53	49	102	0.116[#]	1.483	0.922 to 2.384
	No	89	122	211		Reference	–
Number people at home	< 5	94	98	192	0.13[#]	1.457	0.897 to 2.379
	≥ 5	48	73	121		Reference	–
Maternal education	< 5 years	33	39	72	1[#]	1.009	0.573 to 1.77
	≥ 5 years	109	130	239		Reference	
Previous co-morbidities	Yes	35	14	49	< **0.001**[#]	**3.653**	**1.813** to **0.723**
	No	107	157	264		Reference	–
Time of hospitalization	< 5 days	82	104	186	0.646[#]	0.894	0.555 to 1.471
	≥ 5 days	60	68	128		Reference	
Mechanical ventilation	Yes	22	33	55	0.456[#]	0.773	0.406 to 1.45
	No	120	139	259		Reference	
Death	Yes	0	3	3	0.254[#]	–	–
	No	142	169	311		–	–

Values with positive association are presented in bold. The odds ratio values were based on 2004 cohort. The conditional maximum-likelihood estimate was based on Fisher's Exact test.
[*] χ^2 Test.
[#] Fisher Test.
[¥] Mann-Whitney Test; 95%CI, 95% confidence interval.

Table 2
Viral identification in nasopharyngeal secretion for RSV, respiratory syncytial virus (RSV) in 2004 and 2014 cohorts of Brazilian Infants with acute viral bronchiolitis.

Identification	2004	2014	Total	p-value	Odds ratio	95%CI
RSV positive	47	121	168	< **0.01**[#]	**4.769**	**2.892** to **7.968**
RSV negative	95	51	146		Reference	–
RSV group A	32	8	40	< **0.01**[*]	0.5945	0.221 to 1.434
RSV group B	13	89	102		**16.05**	**0.047** to **34.24**
RSV ND group	121	51	172		Reference	–

ND, non-determined. The odds ratio values were based on 2014 cohort. The conditional maximum-likelihood estimate was based on Fisher's Exact test.
[*] χ^2 test.
[#] Fisher test; 95%CI, confidence interval.

Table 3
Viral identification in nasopharyngeal secretion/frequency of respiratory viruses in 2004 cohort of infants with acute viral bronchiolitis (n = 142).

Viral identification	Frequency (%)
None	88 (62%)
RSV group non determined	26 (18.3%)
RSV group A	13 (9.2%)
RSV group B	7 (4.9%)
Metapneumovirus	7 (4.9%)
RSV group A + metapneumovirus	1 (0.7%)
Total	142 (100%)

RSV, respiratory syncytial virus.

Diagnosis was based on clinical data, which defines AVB as being the first episode of acute respiratory distress with wheezing, preceded by upper airway symptoms such as rhinorrhea and cough, with or without fever [1,5]. The criterion for severe bronchiolitis was oxygen saturation lower than 92%, which demanded oxygen therapy [1]. Exclusion criteria were previous episodes of wheezing. A total of 314 patients were selected (2004: 142; 2014: 172). The studies were approved by the Ethical Committee from University of Campinas [#076/2003 (2004) and #00869612.7.0000.5404 (2014)]. In both cohorts' nasopharyngeal secretions were collected during the first 24 h after hospital admission. In the first cohort, by a washing technique with saline solution followed by aspiration. In the second cohort, collection was done by an aspiration technique without saline solution. Only the described technique for each cohort was accepted. The collected samples were analyzed to viral etiology by Polymerase Chain Reaction (PCR). In the first Cohort, PCR Rt kit (ABI PRISM Big Dye Terminator Cycle Sequencing Ready Reaction kit, Applied Biosystems TM, Foster City, USA) screened RSV and Metapneumovirus [11]; in the second cohort, Seeplex RV15 ACE detection kit (Seegene, Concord, CA) screened 13 types of RNA viruses and two of DNA viruses: RSV subtypes A and B; rhinovirus A/B/C; parainfluenza virus 1, 2, 3, and 4; adenovirus; coronaviruses 229E/NL63 and OC43; influenza A virus and influenza B virus; bocavirus 1/2/3/4; metapneumovirus; and enterovirus. Epidemiologic data [gender, age at attendance, seasonality, gestational age, birth weight, breastfeeding, tobacco exposure, crowding (more than 5 people at home) and maternal education] were analyzed. Clinical data such as previous co-morbidities (lung disease, heart disease, immunodeficiency, undernourishment, Down Syndrome), time of hospitalization, need of mechanical ventilation and death were analyzed and compared in both cohorts. Statistical analysis was performed using the Mann-Whitney, χ^2 and Fisher Exact tests in the Statistical Package for the Social Sciences software, version 24 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Adopted value of significance was 5%.

Table 4
Viral Identification in nasopharyngeal secretion/frequency of respiratory viruses in 2014 cohort of infants with acute viral bronchiolitis (n = 172).

Viral identification without consider RSV groups	Frequency (%)
RSV	87 (50.6%)
Rhinovirus	20 (11.6%)
None	18 (10.5%)
RSV + rhinovirus	17 (9.9%)
Inconclusive	7 (4.1%)
RSV + adenovirus	4 (2,3%)
RSV + hepatitis virus	2 (1,2%)
RSV + parainfluenza virus type 1	2 (1.2%)
RSV + coronavirus 229 E	2 (1.2%)
RSV + rinovirus + adenovirus	2 (1.2%)
Adenovirus	1 (0.6%)
Influenza A virus	1 (0.6%)
Parainfluenza virus type 4	1 (0.6%)
Metapneumovirus	1 (0.6%)
RSV + metapneumovirus	1 (0.6%)
RSV + influenza A virus	1 (0.6%)
RSV + bocavirus	1 (0.6%)
RSV + rhinovirus + metapneumovirus	1 (0.6%)
RSV + rhinovirus + parainfluenza virus type 1	1 (0.6%)
Coronavirus 229E + parainfluenza virus type 3	1 (0.6%)
Rhinovirus + parainfluenza virus type 4	1 (0.6%)
Total	172 (100%)
Viral identification considering RSV groups	**Frequency (%)**
None	18 (10.5%)
RSV group A	66 (38.4%)
Other viruses	25 (15.1%)
RSV group A + other	23 (13.4%)
RSV group B	22 (12.8%)
RSV group B + other	10 (5.8%)
Inconclusive	7 (4.1%)
Total	172 (100%)

RSV, respiratory syncytial virus.

3. Results

Comparison between epidemiologic data is displayed in Table 1; the 2004 cohort presented lower chances of acquiring of AVB in April (OR = 0.538; 95%CI = 0.298 to 0.922), fewer patients with birth weight under 3000 g (OR = 0.276; 95%CI = 0.153 to 0.485) and gestational age < 37 weeks (OR = 0.361; 95%CI = 0.187 to 0.695). In the 2004 cohort (3.5 months), median was attendance age higher than in the 2014 cohort (3 months) (P-value = 0.019). Comparison between clinical data can also be seen in Table 1. In 2004, there was a higher incidence of previous co-morbidities (OR = 3.653; 95%CI = 1.813 to 7.723). No differences were observed regarding time of hospitalization and need of mechanical ventilation. Deaths occurred only in the 2014 cohort (3 patients). In the 2014 cohort there was: (i) higher RSV identification (OR = 4.769; 95%CI = 2.892 to 7.968); (ii) smaller amount of unidentified samples [2014: 25/172 (14.53%); 2004: 88/142 (61.97%); OR = 0.105; 95%CI = 0.058 to 0.185)]; (iii) higher prevalence of RSV-B (OR = 16.05; 95%CI = 0.047 to 34.24) (Table 2). Table 3 shows the frequency of viral types in the 2004 cohort; Table 4 shows the frequency of viral types in the 2014 cohort. Metapneumovirus was identified in 5.6% and 1.7% of patients in 2004 and 2014 cohorts, respectively (p = 0.035; OR = 8.817; 95%CI = 1.111 to 4.019).

4. Discussion

Comparison between the cohorts showed similarities for gender, breastfeeding, tobacco exposure, number of people in home (crowding) and maternal education. In both cohorts, there was a greater number of males, which is comparable what is described in literature [12,13]. Conversely, in the first cohort, the age at attendance was slightly higher; both cohorts had a median of under 4 months of age. Around 30% of patients received breastfeeding for at least one month, in both cohorts. Breastfeeding was considered a protective factor for respiratory infections, and is associated with better clinical evolution [14–16]. Despite stimulus for breastfeeding being on the rise [17], it is not yet a general behavior. Similarly, tobacco exposure has been associated to some respiratory diseases in infants and children. A Brazilian study with 2037 children under 60 months [18] demonstrated that 59.89% (1220/2037) had respiratory symptoms. It was clearly higher among children with passive tobacco exposure (65.53%–504/768) compared to no tobacco exposure children (56.42%–716/1269). In our study, there were lower levels of tobacco exposure and crowding in both cohorts; maternal education was mostly more than 5 years. These similarities can be explained by the economic situation in the studied region, considered the richest in the country, with a Human Development Index comparable to some European regions [19]. In the 2014 cohort, despite some patients coming from private hospitals, it is possible to consider that, in general, all infants had a satisfactory economic condition and similar cultural environment.

AVB prevalence, seasonality, birth weight and gestational age displayed differences between the two cohorts. In the 2014 cohort, there was a higher incidence of AVB in April, more babies with a birth weight < 3000 g and gestational age < 37 weeks. Regarding the higher number of AVB cases in April 2014, the fact that both cohorts had higher number of cases occurred in April, May and June (a typical seasonality previously described) has to be taken into account [11,20,21]. This difference can be attributed to special weather conditions or a different pattern of virus circulation in 2014. Unfortunately, we don't have national data regarding RSV prevalence in 2004 and 2014 to support this claim. Analyzing gestational age and birth weight together, as they can be considered co-dependents (in general, the lower the gestational age is associated with lower birth weight) a mention to specific facts related to the study region are necessary. Brazil is well-known for its high number of cesarean births; in some private medical services, it can reach more than 50% of births which can result in babies with gestational age and birth weight artificially lower than expected [22,23]. Despite a deeper analysis not being carried out, the higher number of patients with birth weight at birth < 3000 g and gestational age < 37 weeks in this second cohort could be explained by the patients from private hospitals. Clinical data were similar in both cohorts regarding time of hospitalization, need of mechanical ventilation and death, also in accordance with literature [24,25]. In the 2004 cohort there were more patients with previous co-morbidities; despite this, no influence was noted in the number of severe cases in this cohort which is the opposite to that described in literature [25].

On regards to virus analysis, different PCR kits were available at each time [8,11], each with different capacities. The kits used in the 2014 cohort made it possible to identify a wider spectrum of respiratory viruses, isolated or in combination. Different rates of virus identification in both cohorts can be attributed to the use of different kits, despite the same technique being used to identify the viruses (PCR). Nonetheless, the difference between the two cohorts also can be attributed to different prevalence of RSV in each year. Studies have been trying to associate the viral type – RSV or other respiratory viruses – with a varying degree of severity in the clinical presentation of AVB. However, the results are still inconclusive [8,10,23]. Similar epidemiologic features (gender, breastfeeding, tobacco exposure, crowding and maternal education) could minimize the impact of these possible risk factors in the analysis of cohort comparison. Differences in seasonality, gestational age and birth weight can be attributed to specific natural, cultural and economic conditions that were not deeply analyzed. Previous co-morbidities were more frequent in the 2004 cohort but had no impact on hospitalization time, need for mechanical ventilation or death. These severity features were similar in both cohorts. Viral type was not related to severity in any cohort. Virology and immunology must be considered, studying genetic variants and the maturation of the

immune system in AVB by RSV or other viruses, mainly in the response to a virus in its initial phase of life [24–27].

Funding

FALM: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for research grants and scholarships #2011/12939-4, #2011/18845-1, #2015/12183-8 and #2015/12858-5; Fundo de Apoio à Pesquisa, ao Ensino e à Extensão da Universidade Estadual de Campinas for research support #0648/2015; JDR: FAPESP for research assistance 2011/18845-1 and #2015/12183-8.

Competing interests

None to be declared.

Ethical approval

The studies were approved by the Ethical Committee from University of Campinas [#076/2003 (2004) and #00869612.7.0000.5404 (2014)].

Acknowledgements

Luciana Helena Antoniassi da Silva and Fernando Rosado Spliki (Veterinarian, PhD in Genetics and Molecular Biology to help in the viral identification.

References

1. S.L. Ralston, A.S. Lieberthal, H.C. Meissner, B.K. Alverson, J.E. Baley, A.M. Gadomski, D.W. Johnson, M.J. Light, N.F. Maraqa, E.A. Mendonca, K.J. Phelan, J.J. Zorc, D. Stanko-Lopp, M.A. Brown, I. Nathanson, E. Rosenblum, S. Sayles 3rd, S. Hernandez-Cancio, American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis, Pediatrics 134 (5) (2014) e1474–e1502, http://dx.doi.org/10.1542/peds.2014-2742.
[2] T. Shi, E. Balsells, E. Wastnedge, R. Singleton, Z.A. Rasmussen, H.J. Zar, B.A. Rath, S.A. Madhi, S. Campbell, L.C. Vaccari, L.R. Bulkow, E.D. Thomas, W. Barnett, C. Hoppe, H. Campbell, H. Nair, Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis, J. Global Health 5 (2) (2015) 020416, http://dx.doi.org/10.7189/jogh.05.020416.
[3] X. Zhan, J.L. Hurwitz, S. Krishnamurthy, T. Takimoto, K. Boyd, R.A. Scroggs, S. Surman, A. Portner, K.S. Slobod, Respiratory syncytial virus (RSV) fusion protein expressed by recombinant Sendai virus elicits B-cell and T-cell responses in cotton rats and confers protection against RSV subtypes A and B, Vaccine 25 (52) (2007) 8782–8793, http://dx.doi.org/10.1016/j.vaccine.2007.10.038.
[4] R. Gilca, G. De Serres, M. Tremblay, M.L. Vachon, E. Leblanc, M.G. Bergeron, P. Dery, G. Boivin, Distribution and clinical impact of human respiratory syncytial virus genotypes in hospitalized children over 2 winter seasons, J. Infect. Dis. 193 (1) (2006) 54–58, http://dx.doi.org/10.1086/498526.
[5] H.C. Meissner, Viral bronchiolitis in children, N. Engl. J. Med. 374 (18) (2016) 1793–1794, http://dx.doi.org/10.1056/NEJMra1413456.
[6] M. Wright, G. Piedmonte, Respiratory syncytial virus prevention and therapy: past, present, and future, Pediatr. Pulmonol. 46 (4) (2011) 324–347, http://dx.doi.org/10.1002/ppul.21377.
[7] M. Lanari, F. Prinelli, F. Adorni, S. Di Santo, S. Vandini, M. Silvestri, M. Musicco, Study group of italian society of neonatology on risk factors for RSV hospitalization. Risk factors for bronchiolitis hospitalization during the first year of life in a multicenter Italian birth cohort, Ital. J. Pediatr. 41 (2015) 40, http://dx.doi.org/10.1186/s13052-015-0149-z.
[8] A.E. Alvarez, F.A.L. Marson, C.S. Bertuzzo, C.W. Arns, J.D. Ribeiro, Epidemiological and genetic characteristics associated with the severity of acute viral bronchiolitis by respiratory syncytial virus, J. Pediatr. (Rio. J) 89 (6) (2013) 531–543, http://dx.doi.org/10.1016/j.jped.2013.02.022.
[9] T.B. Gagliardi, F.E. Paula, M.A. Iwamoto, J.L. Proença-Modena, A.E. Santos, A.A. Camara, M.C. Cervi, O.A. Cintra, E. Arruda, Concurrent detection of other respiratory viruses in children shedding viable human respiratory syncytial virus, J. Med. Virol. 85 (10) (2013) 1852–1859, http://dx.doi.org/10.1002/jmv.23648.
[10] J.O. Wishaupt, T. Ploeg, R. Groot, F.G. Versteegh, N.G. Hartwing, Single- and multiple viral respiratory infections in children: disease and management cannot be related to a specific pathogen, BMC Infect. Dis. (17) (2017) 62, http://dx.doi.org/10.1186/s12879-016-2118-6.
[11] A.G.L. Riccetto, L.H.A. Silva, F.R. Spliki, A.M. Morcillo, C.W. Arns, E.C. Baracat, Genotypes and clinical data of respiratory syncytial virus and metapneumovirus in Brazilian infants: a new perspective, Braz. J. Infect. Dis. 13 (1) (2009) 35–39, http://dx.doi.org/10.1590/S1413-86702009000100008.
[12] E.P. Schlaudecker, J.P. Heck, E.T. Macintyre, R. Martinez, C.N. Dodd, M.M. McNeal, M.A. Staat, J.E. Heck, M.C. Steinhoff, Etiology and seasonality of viral respiratory infections in rural Honduran children, Pediatr. Infect. Dis. J. 31 (11) (2012) 1113–1118, http://dx.doi.org/10.1097/INF.0b013e31826052eb.
[13] D. Zhang, Z. He, L. Xu, X. Zhu, J. Wu, W. Wen, Y. Zheng, Y. Deng, J. Chen, Y. Hu, M. Li, K. Cao, Epidemiology characteristics of respiratory viruses found in children and adults with respiratory tract infections in southern China, Int. J. Infect. Dis. 25 (2014) 159–164, http://dx.doi.org/10.1016/j.ijid.2014.02.019.
[14] M.O. Blanken, H. Koffijberg, E.E. Nibbelke, M.M. Rovers, L. Bont, Duch RSV Neonatal Network. Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study, PLoS One 8 (3) (2013) e59161, http://dx.doi.org/10.1371/journal.pone.0059161.
[15] M. Lanari, F. Prinelli, F. Adorni, S. Di Santo, G. Faldella, M. Silvestri, Musicco M; Italian Neonatology Study Group on RSV Infections. Maternal milk protects infants against bronchiolitis during the first year of life. Results from an Italian cohort of newborns, Early Hum. Dev. 89 (1) (2013) S51–57, http://dx.doi.org/10.1016/S0378-3782(13)70016-1.
[16] C.S. Boccolini, M.L. Carvalho, M.I. Oliveira, M. Boccolini Pde, Breastfeeding can prevent hospitalization for pneumonia among children under 1-year old, J. Pediatr. (Rio J) 87 (5) (2011) 399–404, http://dx.doi.org/10.2223/JPED.2136.
[17] A.M.U. Escobar, A.R. Ogawa, M. Hiratsuka, M.Y. Kawashita, P.Y. Teruya, S. Grisi, S.O. Tomikawa, Breast-feeding and socioeconomic cultural status: factors that lead to early weaning, Rev. Br. Saúde Matern Infant Recife 2 (3) (2002) 253–261, http://dx.doi.org/10.1590/S1519-38292002000300006.
[18] R.M.V. Goncalves-Silva, J.G. Valente, M.G.F. Lemos-Santos, R. Schichieri, Household smoking and respiratory disease in under-five children, Cad Saúde Pública 22 (3) (2006) 579–586, http://dx.doi.org/10.1590/S0102-311X2006000300013.
[19] H.G. Torres, M.P. Ferreira, N.P. Dini, Indicadores sociais: por que construir novos indicadores como o IPRS, São Paulo Perspect. 17 (3-4) (2003) 80–90, http://dx.doi.org/10.1590/S0102-88392003000300009.
[20] F.T. Freitas, Sentinel surveillance of influenza and other respiratory viruses, Brazil, 2000–2010, Braz. J. Infect. Dis. 17 (1) (2013) 62–68, http://dx.doi.org/10.1016/j.bjid.2012.09.001.
[21] J.B. Salomão, L.G. Gardinassi, P.V. Simas, C.O. Bittar, F.P. Souza, P. Rahal, D.M.T. Zanetta, Human respiratory syncytial virus in children hospitalized for acute lower respiratory infection, J. Pediatr. (Rio. J) 87 (3) (2011) 219–224, http://dx.doi.org/10.1590/S0021-75572011000300007.
[22] J.P. Souza, A. Gülmezoglu, P. Lumbiganon, M. Laopaiboon, G. Carroli, B. Fawole, P. Ruyan, WHO Global Survey on Maternal and Perinatal Health Research Group: caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004–2008. WHO global survey on maternal and perinatal health, BMC Med. 8 (2010) 71, http://dx.doi.org/10.1186/1741-7015-8-71.
[23] P. Papoff, C. Moretti, G. Cangiano, E. Bonci, M. Roggini, A. Pierangeli, C. Scagnolari, G. Antonelli, F. Midulla, Incidence and predisposing factors for severe disease in previously healthy term infants experiencing their first episode of bronchiolitis, Acta Paediatr. 100 (7) (2011) e17–23, http://dx.doi.org/10.1111/j.1651-2227.2011.02181.x.
[24] D. Hervás, J. Reina, J.M. Yañez del Valle, J. Figuerola, J.A. Hervás, Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis, Eur. J. Clin. Microbiol. Infect. Dis. 31 (8) (2012) 1975–1981, http://dx.doi.org/10.1007/s10096-011-1529-y.
[25] A.L. Soilly, C. Ferdynus, O. Desplanches, M. Grimaldi, J.B. Gouyon, Paediatric intensive care admissions for respiratory syncytial virus bronchiolitis in France: results of a retrospective survey and evaluation of the validity of a medical information system programme, Epidemiol. Infect. 140 (4) (2012) 608–616, http://dx.doi.org/10.1017/S0950268811001208.
[26] C.M. Tabarani, C.A. Bonville, M. Suryadevara, P. Branigan, D. Wang, D. Huang, H.F. Rosenberg, J.B. Domachowske, Novel inflammatory markers, clinical risk factors and virus type associated with severe respiratory syncytial virus infection, Pediatr. Infect. Dis. J. 32 (12) (2013) e437–442, http://dx.doi.org/10.1097/INF.0b013e3182a14407.
[27] L. Toivonen, J. Vuononvirta, J. Mertsola, M. Waris, Q. He, V. Peltola, Polymorphisms of mannose-Binding lectin and toll-Like receptors 2, 3, 4, 7, and 8 and the risk of respiratory infections and acute otitis media in children, Pediatr. Infect. Dis. J. 36 (5) (2017) e114–e122, http://dx.doi.org/10.1097/INF.0000000000001479.