GIULIANA STRAVINSKAS DURIGON

Bocavírus humano: características clínicas e epidemiológicas em crianças com sintomas respiratórios agudos.

Tese apresentada ao Programa de Pós-Graduação em Microbiologia do Instituto de Ciências Biomédicas da Universidade de São Paulo, para a obtenção do Titulo de Doutor em Ciências.

Área de concentração: Microbiologia

Orientador: Prof. Dr. Edison Luiz Durigon

Versão original

SÃO PAULO
2015

RESUMO

Durigon GS. Bocavírus humano: características clínicas e epidemiológicas em crianças com sintomas respiratórios agudos. [Tese (Doutorado em Microbiologia)]. São Paulo: Instituto de Ciências Biomédicas, Universidade de São Paulo; 2015.

As infecções respiratórias agudas são responsáveis por elevados índices de morbi-mortalidade em todo o mundo. Enquanto o vírus sincicial respiratório (RSV) permanece como a principal causa de infecção do trato respiratório inferior (ITRI) em crianças jovens, especialmente nas menores de 12 meses, outros vírus, como o metapneumovírus humano, vírus influenza, vírus parainfluenza, adenovírus e bocavírus humano (HBoV) estão também associados. Desde sua descoberta em 2005, diversos autores relataram a presença de HBoV em pacientes, na maioria crianças, com doença respiratória aguda, com prevalência variando de 1,5% a 19% nos diferentes estudos ao redor do mundo. Durante o período de estudo (março de 2008 a setembro de 2010) foram detectadas 153 amostras positivas para HBoV (14%) de 1113 amostras coletadas, sendo sete HBoV positivos na unidade neonatal. Dentre as 926 amostras incluídas de crianças da comunidade, o HBoV ocupou a terceira posição em frequência de vírus respiratórios detectados, sendo superado apenas pelo vírus sincicial respiratório e pelo rinovírus . Além de frequente causa de hospitalização, a infecção por HBoV é potencialmente grave. Foi observado que as crianças positivas para HBoV eram significativamente mais velhas (média idade 9,7 meses), utilizaram mais antibióticos, apresentaram o diagnóstico de pneumonia com maior frequência (independente da presença de outros vírus coinfectantes) e o de bronquiolite com menor frequência do que as crianças negativas para HBoV. No total de HBoV positivos, três crianças foram a óbito. O HBoV circulou ao longo de todos os meses estudados , com maior prevalência nos meses de maio a agosto. Houve uma elevada taxa de codetecção com os demais 20 vírus respiratórios pesquisados nas amostras de crianças originadas da comunidade. Apenas 16% dos bocavírus humanos positivos não estavam associados a outros vírus. Rinovírus, adenovírus e RSV, em ordem decrescente, foram os agentes com maior frequência de codetecção. A análise filogenética das amostras positivas para HBoV, demonstrou que foram detectados apenas HBoV1 nas amostras de secreção respiratória de crianças hospitalizadas por ITRI. Esse achado contribuiu para a consolidação do bocavírus humano tipo 1 como causador de doença respiratória aguda na população pediátrica.

Palavras-chave: Vírus. Infecção respiratória. Pediatria. Epidemiologia. Biologia molecular. Diagnóstico.

ABSTRACT

Durigon GS. Human Bocavirus: Clinical and Epidemiological Characteristics in Children with Acute Respiratory Symptoms. [Ph. D. thesis (Microbiology)]. São Paulo: Instituto de Ciências Biomédicas, Universidade de São Paulo; 2015.

It is well established that respiratory viruses are an important cause of hospitalizations in young children worldwide. While respiratory syncytial virus (RSV) remains as leading cause of lower respiratory tract infection (LRTI) in young children, especially those under 12 months, other respiratory viruses, such as human metapneumovirus, influenza, parainfluenza, adenovirus and human bocavirus (HBoV) are also present. Since its discovery in 2005, many authors have reported detection of HBoV in patients with acute respiratory infection, mostly children, with prevalence varying from 1.5% to 19% throughout the world. During the study period (March 2008 to September 2010) we detected HBoV in 153 samples (14%) from 1113-screened samples; seven were from the neonatal unit. Among 926 samples included from children with community-acquired infection, HBoV was the third most frequently detected, just after RSV and rhinovirus. Not only was HBoV a frequent cause of hospitalizations, but also a potentially severe disease. Children infected with HBoV were significantly older (mean age 9.7 months), used more antibiotics, had pneumonia more frequently diagnosed (irrespective of presence of other virus coinfection), and bronchiolitis less frequently diagnosed than those negative for HBoV. In all, three children died. Seasonality of HBoV was characterized by year-round circulation with peaks in months of May through August. There was a high rate of co-detection with the other 20 respiratory viruses screened in samples from the community. Only 16% of the HBoV positives were single infections. Rhinovirus, adenovirus and RSV, in this order, were the most frequently co-detected. Phylogenetic analysis of the HBoV positive samples revealed only HBoV1. This finding contributes to consolidate human bocavirus type 1 as cause of acute respiratory infection in pediatric population.

Keywords: Virus. Respiratory infection. Pediatrics. Epidemiology. Molecular biology. Diagnostics.

1 INTRODUÇÃO

Está bem estabelecido que os vírus respiratórios são causas importantes de morbidade em lactentes de todo o mundo (1). Um grande esforço tem sido feito para melhorar os métodos diagnósticos na tentativa de identificar os agentes etiológicos responsáveis pelas principais síndrome clínicas respiratórias, como a bronquiolite e a pneumonia viral. Enquanto o vírus sincicial respiratório (RSV) permanece como a principal causa de infecção do trato respiratório inferior (ITRI) em crianças jovens, especialmente nas menores de 12 meses (2), outros vírus, como o metapneumovírus humano, vírus influenza, vírus parainfluenza, adenovírus e bocavírus humano (HBoV) estão também associados às ITRI (3).

Desde sua descoberta em 2005, diversos autores relataram a presença de HBoV em pacientes, na maioria crianças, com doença respiratória aguda, com prevalência variando de 1,5% a 19% ao redor do mundo (4).

Entretanto, as síndromes clínicas causadas pelo HBoV em crianças pequenas e a participação desse vírus como agente causador de infecção respiratória aguda grave, resultando em hospitalizações, não está totalmente esclarecida. Tampouco a importância e divergência de comportamento do HBoV em populações com alguma comorbidade, que estão cada vez mais frequentes em nosso meio.

Este estudo tem como objetivo descrever os achados clínicos e epidemiológicos do HBoV em uma vigilância prospectiva de hospitalizações de lactentes menores de dois anos por infecções respiratórias agudas em um hospital terciário na cidade de São Paulo.

7 CONCLUSÕES

Durante o período de estudo (março de 2008 a setembro de 2010) foram detectadas 153 amostras positivas para HBoV (14%) de 1113 amostras coletadas, sendo sete HBoV positivos na unidade neonatal. Dentre as 926 amostras incluídas de crianças da comunidade, o HBoV ocupou a terceira posição em frequência de vírus respiratórios detectados, sendo superado apenas pelo RSV e HRV.

Além de frequente causa de hospitalização, a infecção por HBoV é potencialmente grave. Foi observado que as crianças positivas para HBoV eram significativamente mais velhas (média idade 9,7 meses), utilizaram mais antibióticos, apresentaram o diagnóstico de pneumonia com maior frequência (independente da presença de outros vírus coinfectantes) e o de bronquiolite com menor frequência do que as crianças negativas para HBoV. No total de HBoV positivos, três crianças foram a óbito.

O HBoV circulou ao longo de todos os meses estudados , com maior prevalência nos meses de maio a agosto. Houve uma elevada taxa de codetecção com os demais 20 vírus respiratórios pesquisados nas amostras de crianças originadas da comunidade. Apenas 16% dos bocavírus humanos positivos não estavam associados a outros vírus. Rinovírus, adenovírus e RSV, em ordem decrescente, foram os agentes com maior frequência de codetecção.

A análise filogenética das amostras positivas para HBoV, demonstrou que foram detectados apenas HBoV1 nas amostras de secreção respiratória de crianças hospitalizadas por ITRI. Esse achado contribuiu para a consolidação do bocavírus humano tipo 1 como causador de doença respiratória aguda na população pediátrica.

REFERÊNCIAS*

1. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011; 377(9773):1264–75.

2. Nair H, Nokes J, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375(9725):1545–55.

3. Pavia AT. Viral Infections of the Lower Respiratory Tract: Old Viruses, New Viruses, and the Role of Diagnosis. Clin Infect Dis. 2011;52(4 Suppl):S284–9.

4. Jartti T, Hedman K, Jartti L, Ruuskanen O, Allander T, Söderlund-Venermo M. Human bocavirus-the first 5 years. Rev Med Virol. 2011;22(1):46–64.

5. Langley GF, Anderson LJ. Epidemiology and Prevention of Respiratory Syncytial Virus Infections Among Infants and Young Children. Pediatr Infect Dis J. 2011;30(6):510–7.

6. Mejías A, Chávez-Bueno S, Jafri HS, Ramilo O. Respiratory syncytial virus infections: old challenges and new opportunities. Pediatr Infect Dis J. 2005;24(11 Suppl):S189–97.

7. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2011;12(1):36–44.

8. Eisenberg KW, Szilagyi PG, Fairbrother G, Griffin MR, Staat M, Shone LP, et al. Vaccine Effectiveness Against Laboratory-Confirmed Influenza in Children 6 to 59 Months of Age During the 2003-2004 and 2004-2005 Influenza Seasons. Pediatrics. 2008;122(5):911–9.

9. Resch B, Sommer C, Nuijten MJC, Seidinger S, Walter E, Schoellbauer V, et al. Cost-effectiveness of Palivizumab for Respiratory Syncytial Virus Infection in High-risk Children, Based on Long-term Epidemiologic Data From Austria. Pediatr Infect Dis J. 2012;31(1):e1–e8.

10. Peng D, Zhao D, Liu J, Wang X, Yang K, Xicheng H, et al. Multipathogen infections in hospitalized children with acute respiratory infections. Virol J. 2009;6(1):155–61.

11. Yan Y, Zhang S, Tang Y-W. Molecular Assays for the Detection and Characterization of Respiratory Viruses. Semin Respir Crit Care Med. 2011;32(04):512–26.

12. Murdoch DR, Jennings LC, Bhat N, Anderson TP. Emerging Advances in Rapid Diagnostics of Respiratory Infections. Infectious Disease Clinics of NA. 2010;24(3):791–807.

13. Henrickson KJ. Advances in the laboratory diagnosis of viral respiratory disease. Pediatric Infectious Diseases Journal. 2004;23(1):S6–10.

*De acordo com:
International Committee of Medical Journal Editors. [Internet]. Uniform requirements for manuscripts submitted to biomedical journals. [2011 Jul 15], Available from: http://www.nlm.nih.gov/bsd/uniform_requirements. htlm.

14. Christensen A, Nordbø SA, Krokstad S, Rognlien AGW, Døllner H. Human bocavirus commonly involved in multiple viral airway infections. Journal of Clinical Virology. 2008;41(1):34–7.

15. Lindblom A, Bhadri V, Söderhäll S, Ohrmalm L, Wong M, Norbeck O, et al. Respiratory viruses, a common microbiological finding in neutropenic children with fever. J Clin Virol. 2010;47(3):234–7.

16. Utokaparch S, Marchant D, Gosselink JV, McDonough JE, Thomas EE, Hogg JC, et al. The Relationship Between Respiratory Viral Loads and Diagnosis in Children Presenting to a Pediatric Hospital Emergency Department. Pediatr Infect Dis J. 2011;30(2):e18–e23.

17. Christensen A, Nordbø SA, Krokstad S, Rognlien AGW, Døllner H. Human bocavirus in children: Mono-detection, high viral load and viraemia are associated with respiratory tract infection. Journal of Clinical Virology. 2010;49(3):158–62.

18. Kantola K, Hedman L, Allander T, Jartti T, Lehtinen P, Ruuskanen O, et al. Serodiagnosis of human bocavirus infection. Clin Infect Dis. 2008;46(4):540–6.

19. Aberle JH, Aberle SW, Pracher E, Hutter H-P, Kundi M, Popow-Kraupp T. Single Versus Dual Respiratory Virus Infections in Hospitalized Infants. Pediatr Infect Dis J. 2005;24(7):605–10.

20. Martin ET, Kuypers J, Wald A, Englund JA. Multiple versus single virus respiratory infections: viral load and clinical disease severity in hospitalized children. Influenza and Other Respiratory Viruses. 2011;6(1):71–7.

21. Gurda BL, Parent KN, Bladek H, Sinkovits RS, DiMattia MA, Rence C, et al. Human Bocavirus Capsid Structure: Insights into the Structural Repertoire of the Parvoviridae. Journal of Virology. 2010;84(12):5880–9.

22. Dijkman R, Koekkoek SM, Molenkamp R, Schildgen O, van der Hoek L. Human Bocavirus Can Be Cultured in Differentiated Human Airway Epithelial Cells. Journal of Virology. 2009;83(15):7739–48.

23. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci USA. 2005;102(36):12891–6.

24. Kapoor A, Simmonds P, Slikas E, Li L, Bodhidatta L, Sethabutr O, et al. Human Bocaviruses Are Highly Diverse, Dispersed, Recombination Prone, and Prevalent in Enteric Infections. Journal of Infectious Diseases. 2010;201(11):1633–43.

25. Hirose Y, Hamada H, Wakui T, Ogawa T, Terai M. Characteristic systemic cytokine responses in children with human bocavirus-positive lower respiratory tract infection. Microbiol Immunol. 2014;58(3):215–8.

26. Zhang Z, Zheng Z, Luo H, Meng J, Li H, Li Q, et al. Human Bocavirus NP1 Inhibits IFN-Production by Blocking Association of IFN Regulatory Factor 3 with IFNB Promoter. The Journal of Immunology. 2012 ;189(3):1144–53.

27. Caccia ERB, Watanabe ASA, Carraro E, Leal E, Granato C, Bellei N. Frequency of human bocavirus respiratory infections among at-risk patients in São Paulo, Brazil. Rev Inst Med trop S Paulo. 2012 ;54(6):307–10.
28. Brebion A, Vanlieferinghen P, Dechelotte P, Boutry M, Peigue-Lafeuille H, Henquell C. Fatal Subacute Myocarditis Associated with Human Bocavirus 2 in a 13-Month-Old Child. J Clin Microbiol. 2014;52(3):1006–8.

29. Mori D, Ranawaka U, Yamada K, Rajindrajith S, Miya K, Perera HKK, et al. Human Bocavirus in Patients with Encephalitis, Sri Lanka, 2009–2010. Emerging infectious diseases. 2013;19(11):1859–62.

30. Beder LB, Hotomi M, Ogami M, Yamauchi K, Shimada J, Billal DS, et al. Clinical and microbiological impact of human bocavirus on children with acute otitis media. Eur J Pediatr. 2009;168(11):1365–72.

31. Sadeghi M, Kantola K, Finnegan DPJ, McCaughey C, Hedman L, Soderlund-Venermo M, et al. Possible Involvement of Human Bocavirus 1 in the Death of a Middle-Aged Immunosuppressed Patient. J Clin Microbiol. 2013;51(10):3461–3.

32. Schenk T, Maier B, Hufnagel M, Strahm B, Konty U, Neumann-Haefelin D, et al. Persistence of human bocavirus dna in immunocompromised children. Pediatr Infect Dis J. 2011;30(1):82–4.

33. Schildgen O, Qiu J, Söderlund-Venermo M. Genomic features of the human bocaviruses. Future Virol. 2012;7(1):31–9.

34. Peltola V, Söderlund-Venermo M, Jartti T. Human Bocavirus Infections. Pediatr Infect Dis J. 2013;32(2):178–9.

35. Kantola K, Hedman L, Arthur J, Alibeto A, Delwart E, Jartti T, et al. Seroepidemiology of Human Bocaviruses 1-4. Journal of Infectious Diseases. 2011;204(9):1403–12.

36. Calvo C, García-García ML, Pozo F, Carvajal O, Pérez-Breña P, Casas I. Clinical Characteristics of Human Bocavirus Infections Compared With Other Respiratory Viruses in Spanish Children. Pediatr Infect Dis J. 2008;27(8):677–80.

37. Kesebir D, Vazquez M, Weibel C, Shapiro ED, Ferguson D, Landry ML, et al. Human bocavirus infection in young children in the United States: molecular epidemiological profile and clinical characteristics of a newly emerging respiratory virus. J Infect Dis. 2006;194(9):1276–82.

38. Martins Júnior RB, Carney S, Goldemberg D, Bonine L, Spano LC, Siqueira M, et al. Detection of respiratory viruses by real-time polymerase chain reaction in outpatients with acute respiratory infection. Mem Inst Oswaldo Cruz. 2014;109(6):716–21.

39. da Silva ER, Pitrez PMRC, Arruda E, Mattiello R, Sarria EE, de Paula FVE, et al. Severe lower respiratory tract infection in infants and toddlers from a non-affluent population: viral etiology and co-detection as risk factors. BMC Infectious Diseases; 2013;13(1):1–8.

40. Nascimento-Carvalho CM, Cardoso M-RA, Meriluoto M, Kemppainen K, Kantola K, Ruuskanen O, et al. Human bocavirus infection diagnosed serologically among children admitted to hospital with community-acquired pneumonia in a tropical region. J Med Virol. 2011;84(2):253–8.

41. Bezerra PGM, Britto MCA, Correia JB, Duarte MDCMB, Fonceca AM, Rose K, et al. Viral and Atypical Bacterial Detection in Acute Respiratory Infection in Children Under Five Years. PLoS ONE. 2011;6(4):e18928.

42. Pilger DA, Cantarelli VV, Amantea SL, Leistner-Segal S. Detection of human bocavirus and human metapneumovirus by real-time PCR from patients with respiratory symptoms in Southern Brazil. Mem Inst Oswaldo Cruz. 2011;106(1):56–60.

43. do Amaral de Leon C, Amantea SL, Pilger DA, Cantarelli V. Clinical and epidemiologic profile of lower respiratory tract infections associated with human bocavirus. Pediatr Pulmonol. 2013;48(11):1112–8.

44. Proença-Módena JL, Gagliardi TB, Escremim de Paula F, Iwamoto MA, Criado MF, Camara AA, et al. Detection of Human Bocavirus mRNA in Respiratory Secretions Correlates with High Viral Load and Concurrent Diarrhea. PLoS ONE. 2011;6(6):e21083.

45. Durigon GS, Oliveira DBL, Vollet SB, Storni JG, Felício MCC, Finelli C, et al. Hospital-acquired human bocavirus in infants. Journal of Hospital Infection. 2010;76(2):171–3.

46. Souza EL, Ramos JG, PROENCA-MODENA JL, Diniz A, Carvalho G, Ciuffo I, et al. Human Bocavirus in Very Young Infants Hospitalized with Acute Respiratory Infection in Northeast Brazil. Journal of Tropical Pediatrics. 2010;56(2):125–7.

47. Albuquerque MCM, Varella RB, Santos N. Acute respiratory viral infections in children in Rio de Janeiro and Teresópolis, Brazil. Rev Inst Med trop S Paulo. 2012;54(5):249–55.

48. Gagliardi TB, Iwamoto MA, Paula FE, Proenca-Modena JL, Saranzo AM, Criado MF, et al. Human bocavirus respiratory infections in children. Epidemiol Infect. 2009;137(07):1032-6.

49. Söderlund-Venermo M, Lahtinen A, Jartti T, Hedman L, Kemppainen K, Lehtinen P, et al. Clinical assessment and improved diagnosis of bocavirus-induced wheezing in children, Finland. Emerging infectious diseases. 2009;15(9):1423–30.

50. Hedman L, derlund-Venermo MS, Jartti T, Ruuskanen O, Hedman K. Dating of human bocavirus infection with protein-denaturing IgG-avidity assays—Secondary immune activations are ubiquitous in immunocompetent adults. Journal of Clinical Virology. 2010;48(1):44–8.

51. Don M, Söderlund-Venermo M, Hedman K, Ruuskanen O, Allander T, Korppi M. Don't forget serum in the diagnosis of human bocavirus infection. J Infect Dis. 2011;203(7):1031–3.

52. Deng X, Li Y, Qiu J. Human bocavirus 1 infects commercially available primary human airway epithelium cultures productively. Journal of Virological Methods. 2014;195:112–9.

53. Martin ET, Fairchok MP, Kuypers J, Magaret A, Zerr DM, Wald A, et al. Frequent and Prolonged Shedding of Bocavirus in Young Children Attending Daycare. Journal of Infectious Diseases. 2010;201(11):1625–32.

54. Proenca-Modena JL, Paula FE, Buzatto GP, Carenzi LR, Saturno TH, Prates MC, et al. Hypertrophic Adenoid Is a Major Infection Site of Human Bocavirus 1. J Clin Microbiol. 2014;52(8):3030–7.

55. Lu X, Gooding LR, Erdman DD. Human Bocavirus in Tonsillar Lymphocytes. Emerging infectious diseases. 2008;14(8):1332–3.

56. Proença-Módena JL, Buzatto GP, Paula FE, Saturno TH, Delcaro LS, Prates MC, et al. Respiratory viruses are continuously detected in children with chronic tonsillitis throughout the year. International Journal of Pediatric Otorhinolaryngology. 2014;78(10):1655–61.

57. Kantola K, Sadeghi M, Antikainen J, Kirveskari J, Delwart E, Hedman K, et al. Real-time quantitative PCR detection of four human bocaviruses. J Clin Microbiol. 2010;48(11):4044–50.

58. Manning A, Russell V, Eastick K, Leadbetter GH, Hallam N, Templeton K, et al. Epidemiological profile and clinical associations of human bocavirus and other human parvoviruses. J Infect Dis. 2006;194(9):1283–90.

59. Hindiyeh MY, Keller N, Mandelboim M, Ram D, Rubinov J, Regev L, et al. High rate of human bocavirus and adenovirus coinfection in hospitalized Israeli children. J Clin Microbiol. 2008;46(1):334-37.

60. Chen L, Yao Q, Ma J, Li J, Zhang Q, Yang Y, et al. A novel integrated strategy for detection of human bocavirus based on a heminested PCR assay combined with boiling lysis method of samples in human specimens. Journal of Virological Methods. 2014;203:48–53.

61. Sloots T, Mcerlean P, Speicher D, Arden K, Nissen M, Mackay I. Evidence of human coronavirus HKU1 and human bocavirus in Australian children. Journal of Clinical Virology. 2006;35(1):99–102.

62. Schildgen O, Müller A, Allander T, Mackay IM, Völz S, Kupfer B, et al. Human bocavirus: passenger or pathogen in acute respiratory tract infections? Clin Microbiol Rev. 2008;21(2):291–304.

63. Martin ET, Kuypers J, McRoberts JP, Englund JA, Zerr DM. Human Bocavirus 1 Primary Infection and Shedding in Infants. Journal of Infectious Diseases. 2015; Jan 28 [Epub ahead of print].

64. Allander T, Jartti T, Gupta S, Niesters HGM, Lehtinen P, Osterback R, et al. Human bocavirus and acute wheezing in children. Clin Infect Dis. 2007;44(7):904–10.

65. Christensen A, Døllner H, Skanke LH, Krokstad S, Moe N, Nordbø SA. Detection of spliced mRNA from human bocavirus 1 in clinical samples from children with respiratory tract infections. Emerging infectious diseases. 2013;19(4):574–80.

66. Court SDM. The definition of acute respiratory illnesses in children. Postgraduate Medical Journal. 1973;49:771–6.
67. Bordley WCW, Viswanathan MM, Lohr KNK, 7. Diagnosis and testing in bronchiolitis: a systematic review. Arch Pediatr Adolesc Med. 2004;158(2):119–26.

68. Dare RK, Fry AM, Chittaganpitch M, Sawanpanyalert P, Olsen SJ, Erdman DD. Human Coronavirus Infections in Rural Thailand: A Comprehensive Study Using Real-Time Reverse-Transcription Polymerase Chain Reaction Assays. Journal of Infectious Diseases. 2007;196(9):1321–8.

69. Kodani M, Yang G, Conklin LM, Travis TC, Whitney CG, Anderson LJ, et al. Application of TaqMan Low-Density Arrays for Simultaneous Detection of Multiple Respiratory Pathogens. J Clin Microbiol. 2011;49(6):2175–82.

70. Fry AM, Lu X, Chittaganpitch M, Peret T, Fischer J, Dowell SF, et al. Human Bocavirus: A Novel Parvovirus Epidemiologically Associated with Pneumonia Requiring Hospitalization in Thailand. Journal of Infectious Diseases. 2007;195(7):1038–45.

71. Lu X, Chittaganpitch M, Olsen SJ, Mackay IM, Sloots TP, Fry AM, et al. Real-Time PCR Assays for Detection of Bocavirus in Human Specimens. J Clin Microbiol. 2006;44(9):3231–5.

72. Lu X, Holloway B, Dare RK, Kuypers J, Yagi S, Williams JV, et al. Real-Time Reverse Transcription-PCR Assay for Comprehensive Detection of Human Rhinoviruses. J Clin Microbiol. 2008;46(2):533–9.

73. Heim A, Ebnet C, Harste G, Pring-Åkerblom P. Rapid and quantitative detection of human adenovirus DNA by real-time PCR. J Med Virol. 2003;70(2):228–39.

74. Morgan OW, Chittaganpitch M, Clague B, Chantra S, Sanasuttipun W, Prapasiri P, et al. Hospitalization due to human parainfluenza virus-associated lower respiratory tract illness in rural Thailand. Influenza and Other Respiratory Viruses. 2012;7(3):280–5.

75. Woo PCY, Lau SKP, Chu CM, Chan KH, Tsoi HW, Huang Y, et al. Characterization and Complete Genome Sequence of a Novel Coronavirus, Coronavirus HKU1, from Patients with Pneumonia. Journal of Virology. 2005;79(2):884–95.

76. Hahsler M, Grun B, Hornik K. arules – A Computational Environment for Mining Association Rules and Frequent Item Sets. Journal of Statistical Software. 2005;14(15):1–25.

77. R Development Core Team. R: A Language and Environment for Statistical Computing. [Internet]. Vienna: R Foundation for Statistical Computing; 2005 Jan. Available from: http:// http: //www.R-project.org/. [Acessado em 10 de junho de 2015].

78. Zhang C, Zhu N, Xie Z, Lu R, He B, Liu C, et al. Viral Etiology and Clinical Profiles of Children with Severe Acute Respiratory Infections in China. PLoS ONE. 2013;8(8):e72606.

79. Durigon GS, Oliveira DBL, Felicio MCC, Finelli C, Pereira MFB, Storni JG, et al. Poor Outcome of Acute Respiratory Infection in Young Children with Underlying Health Condition in Brazil. International Journal of Infectious diseases. 2015;34:3–7.
80. Sly PD, Jones CM. Viral co-detection in infants hospitalized with respiratory disease: is it important to detect? J Pediatr (Rio J). 2011;87(4): 277-80.

81. Chorazy ML, Lebeck MG, McCarthy TA, Richter SS, Torner JC, Gray GC. Polymicrobial Acute Respiratory Infections in a Hospital-based Pediatric Population. Pediatr Infect Dis J. 2013;32(5):460–6.

82. Cilla G, Oñate E, Perez-Yarza EG, Montes M, Vicente D, Perez-Trallero E. Viruses in community-acquired pneumonia in children aged less than 3 years old: High rate of viral coinfection. J Med Virol. 2008;80(10):1843–9.

83. Calvo C, García-García ML, Blanco C, Vázquez MC, Frías ME, Pérez-Breña P, et al. Multiple simultaneous viral infections in infants with acute respiratory tract infections in Spain. Journal of Clinical Virology. 2008;42(3):268–72.

84. Marguet C, Lubrano M, Gueudin M, Le Roux P, Deschildre A, Forget C, et al. In Very Young Infants Severity of Acute Bronchiolitis Depends On Carried Viruses. PLoS ONE. 2009;4(2):e4596.

85. Ferraro AA, Ferronato AE, Sacramento PICRD, Botosso VF, Oliveira DBL de, Marinheiro JC, et al. Severity of viral coinfection in hospitalized infants with respiratory syncytial virus infection. J Pediatr (Rio J). 2011;87 (4): 1-7.

86. Nascimento MS, Souza AV de, Ferreira AV de S, Rodrigues JC, Abramovici S, Silva Filho LVFD. High rate of viral identification and coinfections in infants with acute bronchiolitis. Clinics. 2010;65(11):1133–7.

87. Stempel HE, Martin ET, Kuypers J, Englund JA, Zerr DM. Multiple viral respiratory pathogens in children with bronchiolitis. Acta Paediatrica. 2009;98(1):123–6.

88. Bonzel L, Tenenbaum T, Schroten H, Schildgen O, Schweitzer-Krantz S, Adams O. Frequent Detection of Viral Coinfection in Children Hospitalized With Acute Respiratory Tract Infection Using a Real-Time Polymerase Chain Reaction. Pediatr Infect Dis J. 2008;27(7):589–94.

89. Cantais A, Mory O, Pillet S, Verhoeven PO, Bonneau J, Patural H, et al. Epidemiology and microbiological investigations of community-acquired pneumonia in children admitted at the emergency department of a university hospital. Journal of Clinical Virology. 2014;60(4):402–7.

90. Ahn JG, Choi SY, Kim DS, Kim KH. Human bocavirus isolated from children with acute respiratory tract infections in Korea, 2010-2011. J Med Virol. 2014;86:2011-18.

91. Esposito S, Daleno C, Prunotto G, Scala A, Tagliabue C, Borzani I, et al. Impact of viral infections in children with community-acquired pneumonia: results of a study of 17 respiratory viruses. Influenza and Other Respiratory Viruses. 2012;7(1):18–26.

92. Hasan R, Rhodes J, Thamthitiwat S, Olsen SJ, Prapasiri P, Naorat S, et al. Incidence and Etiology of Acute Lower Respiratory Tract Infections in Hospitalized Children Younger Than 5 Years in Rural Thailand. Pediatr Infect Dis J. 2014;33(2):e45–e52.
93. Nunes MC, Kuschner Z, Rabede Z, Madimabe R, Van Niekerk N, Moloi J, et al. Clinical Epidemiology of Bocavirus, Rhinovirus, Two Polyomaviruses and Four Coronaviruses in HIV-Infected and HIV-Uninfected South African Children. PLoS ONE. 2014;9(2):e86448.

94. Uršič T, Jevšnik M, Žigon N, Krivec U, Beden AB, Praprotnik M, et al. Human bocavirus and other respiratory viral infections in a 2-year cohort of hospitalized children. J Med Virol. 2011;84(1):99–108.

95. Piotrowska Z, Vazquez M, Shapiro ED, Weibel C, Ferguson D, Landry ML, et al. Rhinoviruses Are a Major Cause of Wheezing and Hospitalization in Children Less Than 2 Years of Age. Pediatr Infect Dis J. 2008;28(1):25–9.

96. Deng Y, Gu X, Zhao X, Luo J, Luo Z, Wang L, et al. High Viral Load of Human Bocavirus Correlates with Duration of Wheezing in Children with Severe Lower Respiratory Tract Infection. PLoS ONE. 2012;7(3):e34353.

97. Smit PM, Pronk SM, Kaandorp JC, Weijer O, Lauw FN, Smits PHM, et al. RT-PCR detection of respiratory pathogens in newborn children admitted to a neonatal medium care unit. Pediatr Res. 2012;73(3):355–61.

98. Nascimento-Carvalho CM, Ribeiro C, Cardoso M-RA, Barral A, Araújo-Neto CA, Oliveira JR, et al. The Role of Respiratory Viral Infections Among Children Hospitalized for Community-Acquired Pneumonia in a Developing Country. Pediatr Infect Dis J. 2008;27(10):939–41.

99. Wang M, Cai F, Wu X, Wu T, Su X, Shi Y. Incidence of viral infection detected by PCR and real-time PCR in childhood community-acquired pneumonia: A meta-analysis. Respirology. 2015;20(3):405–12.

100. García-García ML, Calvo C, Pozo F, Villadangos PA, Pérez-Breña P, Casas I. Spectrum of Respiratory Viruses in Children With Community-acquired Pneumonia. Pediatr Infect Dis J. 2012;31(8):808–13.

101. World Health Organization. Pneumonia. WHO Fact Sheet [Internet]. 331st ed. Geneva; 2014 Nov 1;1–5. Available from: http://www.who.int/mediacentre/facsheets/fs331/en

102. Maakaroun NR, Moanna A, Jacob JT, Albrecht H. Viral infections associated with haemophagocytic syndrome. Rev Med Virol. 2010;20(2):93–105.

103. Usmani GN, Woda BA, Newburger PE. Advances in understanding the pathogenesis of HLH. Br J Haematol. 2013;161(5):609–22.

104. Ansuini V, Rigante D, Esposito S. Debate around infection-dependent hemophagocytic syndrome in paediatrics. BMC Infectious Diseases. 2013;13(1):15-23.

105. Kerr JR. A review of blood diseases and cytopenias associated with human parvovirus B19 infection. Rev Med Virol. 2015 May 11; [Epub].

106. Shrestha B, Omran A, Rong P, Wang W. Report of a Fatal Pediatric Case of Hemophagocytic Lymphohistiocytosis Associated with Pandemic Influenza A (H1N1) Infection in 2009. Pediatrics and Neonatology. 2015;56(3):189–92.

107. Beffermann N, Pilcante J, Sarmiento M. Acquired hemophagocytic syndrome related to parainfluenza virus infection: case report. Journal of Medical Case Reports. 2015;9(78):1–5.

108. Smith JG, Wiethoff CM, Stewart PL, Nemerow GR. Adenovirus. Curr Top Microbiol Immunol. Curr Top Microbiol Immunol; 2010;343:195–224.

109. Calvo C, García-García ML, Blanco C, Santos MJ, Pozo F, Pérez-Breña P, et al. Human bocavirus infection in a neonatal intensive care unit. Journal of Infection. 2008;57(3):269–71.

110. Piralla A, Lunghi G, Percivalle E, Viganò C, Nasta T, Pugni L, et al. FilmArray® respiratory panel performance in respiratory samples from neonatal care units. Diagnostic Microbiology and Infectious Disease. Elsevier Inc; 2014;79(2):183–6.

111. Chieochansin T, Kapoor A, Delwart E, Poovorawan Y, Simmonds P. Absence of Detectable Replication of Human Bocavirus Species 2 in Respiratory Tract. Emerging infectious diseases. 2009;15(9):1503–5.

112. Han T-H, Chung J-Y, Hwang E-S. Human Bocavirus 2 in Children, South Korea. Emerging infectious diseases. 2009;15(10):1699–700.

113. Song J-R, Jin Y, Xie Z-P, Gao H-C, Xiao N-G, Chen W-X, et al. Novel Human Bocavirus in Children with Acute Respiratory Tract Infection. Emerging infectious diseases. 2010;16(2):324–7.

114. Koseki N, Teramoto S, Kaiho M, Gomi-Endo R, Yoshioka M, Takahashi Y, et al. Detection of Human Bocaviruses 1 to 4 from Nasopharyngeal Swab Samples Collected from Patients with Respiratory Tract Infections. J Clin Microbiol. 2012;50(6):2118–21.