

# Adenoviruses and acute respiratory infections in children living in an equatorial area of Brazil

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Received 17 April 2014; Final revision 27 March 2015; Accepted 15 April 2015;  
first published online 26 June 2015

## SUMMARY

Human adenoviruses (HAdVs) are important respiratory pathogens, found in 2–27% of acute respiratory infection (ARI) cases. Few studies have analysed the diversity of species and types of HAdVs associated with ARI in Brazil. The purpose of this study was to determine the circulation patterns of the different HAdV species and respective types associated with ARI in children in the city of Fortaleza, northeastern Brazil. HAdVs were screened by an indirect immunofluorescence assay, and subsequently identified as species and types by PCR and sequencing of the hexon gene (HVR1–HVR6). Between 2001 and 2013, a total of 290 HAdV strains were detected, 190 of which were identified as belonging to the HAdV-B, -C and -E species. Seven types of HAdVs circulated in the studied population during the analysed period, with HAdV-3 being predominant.

**Key words:** Adenoviruses, molecular epidemiology, respiratory infections, surveillance.

## INTRODUCTION

Human adenoviruses (HAdVs) are associated with clinical syndromes involving various systems, such as respiratory, gastrointestinal and urinary [1–3]. Taxonomically, HAdVs belong to the family Adenoviridae, genus *Mastadenovirus* and are divided into seven species (HAdV-A to G) and 54 types. They are non-enveloped viruses with icosahedral symmetry and a genome composed of a double-strand of linear DNA [4, 5]. Different species and types of HAdVs have tropism for a wide range of body tissues. In this context HAdV-C, types 1, 2, 5 and 6, and HAdV-B, types 3 and 7 are frequently associated with respiratory infections during childhood, which can vary from mild to severe [3, 6].

Ongoing surveillance of HAdVs can reveal their circulation pattern in a particular region and the emergence of the types associated with milder or more serious childhood infections [7, 8]. The main aims of this article are to describe the clinical-epidemiological profile of acute respiratory infection (ARI) caused by HAdVs in children treated at a hospital in Fortaleza from 2001 to 2013 and to characterize the species and type of the circulating HAdVs from 2001 to 2011.

## MATERIALS AND METHODS

### Study location

The study was conducted in Fortaleza, capital of the state of Ceará, northeastern Brazil, located 4° south of the equator, at sea level. This city has a population of 2 500 000 inhabitants. It presents high relative humidity (>70%), little variation in average temperature

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over the course of the year (26–28 °C) and the major climatic variable is the rainy season that occurs during 3–5 months, generally from February to June. The samples were collected from children of any age treated in the emergency room or wards of Hospital Infantil Albert Sabin (HIAS), a reference paediatric hospital that cares for more than 150 000 children per year.

### Demographic and clinical data

All children of any age with ARI symptoms [cough, rhinitis, sore throat, earache, dyspnoea and/or fever ( $\geq 37.5$  °C)] within 7 days of onset, were included in the study if their parents/guardians signed an informed consent. The clinical diagnosis was made by the attending physician of each child. The age, gender, signs, symptoms, clinical diagnosis of each child as well the date the sample was collected were included in the study and recorded on a standard form and later transferred to an Excel file. No follow-up was performed. Medical charts of hospitalized patients were reviewed for more detailed demographic and clinical data. This project was approved by the HIAS Ethical and Research Committee (Register 13/06).

### Laboratory procedures

Nasopharyngeal aspirate was obtained from each participating child. The samples were collected from Monday to Friday from January 2001 to June 2013. Each sample was conserved on ice until processing in the Virology Laboratory of the Federal University of Ceará. Each nasopharyngeal sample was placed in 2 ml virus transport medium (Eagle's minimal essential medium plus 100 U penicillin and 50 mg gentamicin); in the laboratory samples were divided into two 1-ml aliquots. One aliquot was processed for indirect immunofluorescence assay (IFA) and the other was stored at -86 °C for later biology molecular studies. IFA was performed for all samples collected from 2001 to 2013, using the Respiratory Viral Panel I Screening and Identification kit (Chemicon, Light Diagnostics, USA), to search for antigens of the influenza A and B virus, respiratory syncytial virus (RSV), HAdV and parainfluenza virus (PIV) types 1, 2 and 3, according to the manufacturer's protocol. Human metapneumovirus was searched for only in samples collected from 2006 to 2008 using the Human Metapneumovirus Direct Immunofluorescence Assay Reagent (Chemicon, Light Diagnostics).

### Molecular typing of HAdVs

All samples collected from 2001 to 2011 that tested positive for HAdV by IFA, were sent to the Adenovirus Molecular Biology Laboratory of the University of São Paulo (USP) to identify the species and types. The viral DNA was extracted following the protocol described by Shinagawa *et al.* [9]. The species and types were identified by the protocol of Lu & Erdman [10], which consists of polymerase chain reaction (PCR) with primers targeted at the hypervariable regions of the hexon gene (HVR1–HVR6), followed by sequencing of the amplicon, with the ABI Prism 3100 Genetic Analyser (Applied Biosystems, USA). The obtained sequences were edited by Sequencher (Gene Codes Corporation, USA) and identified by NCBI BLAST, by comparing them against those already available in its online database (<http://www.ncbi.nlm.nih.gov/blast/Blast.cgi?PAGE=Nucleotides>).

### Statistical analysis

Descriptive statistics were used for univariate analysis. Fisher's exact test, Spearman's correlation and odds ratio (OR) test were applied to the data using SPSS software (SPSS Inc., USA). All *P* values were considered significant at  $P \leq 0.05$ .

## RESULTS

Between January 2001 and June 2013, 8517 samples were collected and submitted for IFA. At least one of the searched viruses was detected in 2467 (29.97%) of the samples. HAdVs were detected in 290 (11.76%) of all samples that tested positive for viruses, representing 3.41% of the total ARI cases. HAdV was the most frequent virus in co-detections (OR 5.01,  $P < 0.05$ ). In 56 HAdV-positive samples another virus was also detected. In four other positive samples, two different viruses were also present. The most frequently detected virus in these cases was RSV, with 24 (40.0%) cases, followed by influenza with 17 (28.33%) cases.

The characteristics of the studied population are reported in Table 1. Respiratory infections caused by HAdVs was most frequent (73.4%) in children up to age 2 years. In this age group, the detection of HAdVs was higher in children in the second year of life [ $24.52 \pm 3.29$  months, 95% confidence interval (CI) 1.31, range 1–179 months]. Upper respiratory tract infection (URTI) and pneumonia were the

Table 1. *Clinical and demographic details of the patients*

Characteristics	HAdV+ (%)	HadV- (%)	OR (95% CI)	<i>P</i> value
Gender				
Male	166 (57.24)	4696 (57.08)	1.00 (0.79–1.27)	0.95
Female	124 (42.76)	3531 (42.92)		
Age (months)				
0–12	122 (42.07)	3658 (44.46)	0.90 (0.71–1.49)	0.42
13–24	91 (31.38)	2119 (25.75)	1.31 (1.02–1.69)	<b>0.03</b>
25–36	33 (11.38)	982 (11.94)	0.94 (0.65–1.37)	0.77
37–48	16 (5.52)	460 (5.59)	0.98 (0.59–1.64)	0.95
49–60	7 (2.41)	258 (3.14)	0.76 (0.35–1.63)	0.48
>60	21 (7.24)	750 (9.12)	0.77 (0.49–1.22)	0.27
Diagnostic				
URTI	155 (53.45)	3870 (47.04)	1.29 (1.02–1.63)	<b>0.03</b>
Pneumonia	79 (27.24)	1818 (22.10)	1.31 (1.01–1.71)	<b>0.03</b>
Bronchitis	7 (2.41)	345 (4.19)	0.56 (0.26–1.20)	0.13
Bronchiolitis	23 (7.93)	955 (11.61)	0.65 (0.42–1.00)	0.05
Asthma exacerbation	26 (8.97)	1239 (15.06)	0.55 (0.36–0.83)	<b>0.00</b>
Place of attendance				
Emergency room	233 (80.33)	6865 (83.44)	1.23 (0.91–1.65)	0.16
Ward	57 (19.66)	1164 (16.56)		

HAdV, Human adenovirus; OR, odds ratio; CI, confidence interval; URTI, upper respiratory tract infection.

syndromes most often associated with HAdVs, accounting for 53.45% and 27.24% of the cases, respectively. In both types of infection, there was a strong significant association with the presence of HAdVs. By contrast, the detection of HAdVs in cases of asthma exacerbation was lower than other viruses. The risk of the patients with ARI-positive HAdVs was almost half of the risk presented by patients infected with other viruses (OR 0.55,  $P < 0.01$ ).

HAdVs were detected in only 15.86% of the children who required hospitalization, and the most frequent diagnosis in these cases were bronchiolitis (37%) and pneumonia (30.43%).

We observed two annual peaks of ARI, the highest peak in the first half of the year, associated with the rainy season (Spearman correlation,  $P < 0.05$ ), and the lowest peak occurring in the second half of the year. HAdV-positive ARI cases occurred all year round. They were not related to the rainy season (Spearman's correlation,  $P > 0.05$ ). The number of HAdVs detected per year ranged from three (2012) to 48 cases (2013). Although there are no regular epidemic periods of HAdV in Fortaleza, the months with the highest prevalence were September and October (OR 1.87, 95% CI 1.41–2.49,  $P < 0.0001$ ) (Fig. 1).

Sequences were obtained from 65.52% of the analysed HAdVs. It was possible to determine the species

and types of 189 strains, with only one remaining unidentified. Three species were found: HAdV-B (162, 85.72%), HAdV-C (21, 11.11%) and HAdV-E (6, 3.17%). The predominant types were HAdV-3 and HAdV-7, present in 128 (67.72%) and 34 (18.00%) samples, respectively, followed by HAdV-1 and HAdV-2, identified in eight samples (4.24%) each, while HAdV-4 was detected in six (3.17%) samples (Table 2). Of the typed HAdVs, 22 were from hospitalized patients, with HAdV-3 and HAdV-7 identified in 15 (68.18%) and four (18.18%) of the cases, respectively. In the other three cases found in hospitalized patients, HAdV-1, HAdV-2 and HAdV-4 were detected.

The different types were not evenly distributed throughout in the years. The only type present in all years was HAdV-3. HAdV-7 was not detected in 2006, 2010 and 2011, while the other types identified were distributed irregularly. HAdV-2 and HAdV-4 were first detected in 2007 (Table 2).

## DISCUSSION

The low detection rate of HAdVs in this study is similar to findings of other studies using IFA to detect HAdVs [11, 12] but far below the results of Brazilian studies that have used molecular methods such as PCR for viral detection [13, 14]. Those

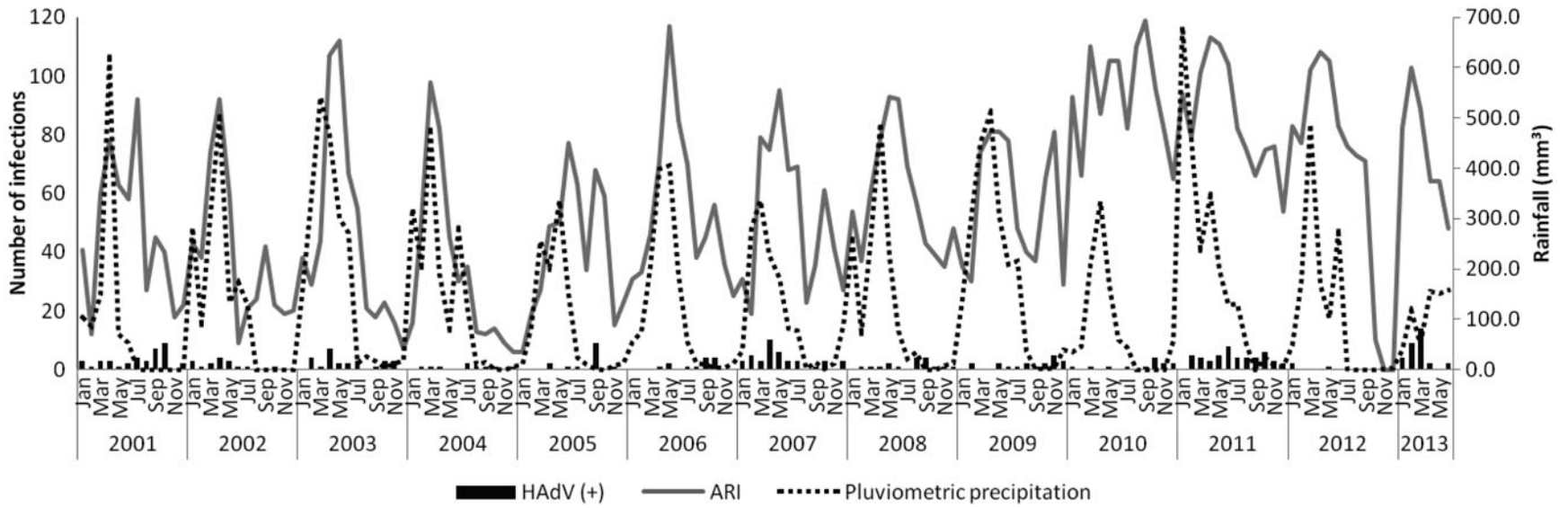


Fig. 1. Monthly distribution of total acute respiratory infections (ARIs), those due to adenovirus and rainfall, Fortaleza, Brazil, January 2001 to June 2013.

Table 2. Distribution of all samples, adenovirus-positive samples by indirect immunofluorescence, and species and types of adenovirus by year (2001–2011)

Year	Total samples	Samples HAdV+ by IFA (%)	Species/types											
			Species			HAdV-B			HAdV-C			HAdV-E		
			HAdV-B	HAdV-C	HAdV-E	3 (%)	7 (%)	1 (%)	2 (%)	5 (%)	6 (%)	4 (%)		
2001	556	39 (7.01)	20 (86.96)	3 (13.04)	0	10 (43.48)	2 (8.7)	0	1 (4.34)	0	0			
2002	463	17 (3.67)	14 (100)	0	9 (64.29)	5 (35.71)	0	0	0	0	0			
2003	537	26 (4.84)	22 (95.65)	1 (4.35)	17 (73.91)	5 (21.74)	1 (4.35)	0	0	0	0			
2004	411	9 (2.19)	7 (100)	0	5 (71.43)	2 (28.57)	0	0	0	0	0			
2005	490	14 (2.86)	12 (92.31)	1 (7.69)	7 (53.85)	5 (38.46)	1 (7.69)	0	0	0	0			
2006	653	13 (2.00)	12 (92.31)	1 (7.69)	0	12 (92.31)	0	0	1 (7.69)	0	0			
2007	624	40 (6.41)	33 (86.84)	2 (5.26)	3 (8.90)	28 (73.69)	1 (2.63)	1 (2.63)	0	0	3 (7.89)			
2008	706	18 (2.55)	12 (80)	1 (6.67)	2 (13.33)	11 (73.33)	1 (6.67)	0	0	0	2 (13.33)			
2009	679	19 (2.80)	16 (94.12)	1 (5.88)	0	15 (88.24)	1 (5.88)	0	1 (5.88)	0	0			
2010	1119	13 (1.16)	6 (66.67)	2 (22.22)	1 (11.11)	6 (66.67)	0	0	2 (22.22)	0	1 (11.11)			
2011	1030	48 (4.66)	8 (47.06)	9 (52.94)	0	8 (47.06)	0	2 (11.76)	4 (23.54)	2 (11.76)	1 (5.88)			
Total	7268	256 (3.52)	162 (85.72)	21 (11.11)	6 (3.17)	128 (67.72)	34 (18)	8 (4.24)	8 (4.24)	4 (2.12)	1 (0.6)	6 (3.18)		

HAdV, Human adenovirus; IFA, indirect immunofluorescence assay.

methods generally are much more sensitive than IFA in relation to HAdVs, but IFA continues to be widely used by the health surveillance authorities in many countries, including Brazil, because of its low cost and ease of application [15, 16]. In the set of analysed samples, HAdVs were only the fourth leading virus detected, exceeded by RSV, PIV-3 and influenza A. Higher HAdV detection rates have been reported in some studies performed exclusively with hospitalized patients [17, 18], although a lower rate was reported in one study with inpatients even when PCR was used to search for HAdVs [19]. The detection of HAdVs in co-infections is commonly reported, at times at higher rates than we found [6, 14, 20, 21]. In addition there are reports of detection of HAdVs in the airways of children without respiratory symptoms and prolonged release of these viruses after infection [22–24].

In the present study respiratory infections in which HAdVs were detected occurred predominately in males. Some studies show similar results with other agents, which emphasize that in the early stages of life, morbidity and mortality in males is higher [18, 25–27]. Regarding age, there was a reduction in the frequency of detection of HAdVs in children aged >2 years, as reported in several studies [28–30].

The infections that occurred in HAdV-positive cases in the present study were diagnosed mainly as URTI and pneumonia, similar to the observations in many other studies [11, 31]. The cases of pneumonia associated with HAdVs in the present study were observed mainly in patients who received treatment in the emergency room but did not need hospitalization, so that treatment occurred at home. Because we did not perform any follow-up of these patients, we could not assess the evolution of pneumonia cases in these patients. None of the children who were hospitalized with pneumonia died.

The main climate change during the year in Fortaleza is the rainy season. Previous studies have demonstrated an association between the rainy season and epidemic periods of RSV and influenza, but this did not occur with HAdVs in our study [32, 33]. In addition, the correlation between the occurrence of the PIV-3 and the dry season, reported in other studies [32, 34], was not observed with HAdVs, even though the detection rates of these viruses were highest in the dry months of September and October. Therefore, the distribution of ARIs associated with HAdVs in Fortaleza occurs throughout the year, as reported in various studies conducted in equatorial regions as well as temperate ones [14, 35–39].



Much remains to be clarified about the activity of the various HAdV types associated with respiratory infections in Brazil, especially in the northeastern region, where only one previous study has been published [35]. The analysis of the species and types of HAdVs present in Fortaleza between 2001 and 2011 shows that three species circulate (HAdV-A, -B, -E), with HAdV-B predominating in all years except 2011, when HAdV-C was most prevalent. The predominance of HAdV-B type 3, observed in this study, is similar to that reported in recent studies in Colombia and South Korea [36, 37]. Predominance of HAdV-B has also been reported in Argentina in a study that analysed the circulation of HAdV from 1999 to 2010, although the main type in that country was found to be HAdV-7 [12]. In Salvador, near Fortaleza, a study of the circulating HAdVs in 1998 showed the predominance of HAdV-C [35]. In turn, in southeastern Brazil there are reports of the predominant circulation of HAdV-C [11] and HAdV-B, with type 7 being the major type [17]. Higher prevalence of HAdV-C over HAdV-B has been reported in many other Latin American countries [6, 39]. In relation to the activity of the HAdV-C types in Fortaleza, we observed a maximum of two circulating types, and in the majority of cases only one type was detected. This differs considerably from the findings of a study conducted in the city of Salvador, where a greater diversity of HAdV-C types was reported, but only in one year [36]. In Fortaleza, the circulation of four different HAdV-C types was found only in 2013.

The HAdV-4 virus, the only human representative of the HAdV-E species, has often been associated with ARIs in American soldiers [40], but this type has been detected in the paediatric population at relatively lower rates than other serotypes, as occurred in this and other studies [41]. Of the HAdVs circulating in Fortaleza, this type was first detected in samples collected in 2007, from children with URTI (two cases), pneumonia (three cases) and aggravated asthma (one case). However, it had already been detected in the nasopharyngeal secretion of a child with ARI in the state of Minas Gerais (southeastern Brazil) in 2002 [11].

Limitations of this study include the low number of HAdVs analysed, an expected result based on the low sensitivity of IFA, and the molecular analysis (types and species) of only 65% of the detected HAdVs, due to the need to transport the samples for analysis to another laboratory.

In conclusion, we identified seven different types of HAdVs in the paediatric population of Fortaleza, associated with different respiratory complaints, over a period of 11 years. However, for better knowledge of the circulation of HAdVs, continued surveillance and the use of more sensitive methods to detect these viruses are needed.

## ACKNOWLEDGEMENTS

This study was supported by the Departamento de Ciência e Tecnologia (DECIT)/Secretaria de Ciência, Tecnologia e Insumos Estratégicos (SCTIE)/Ministério da Saúde, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (FUNCAP) and Secretária de Saúde do Estado do Ceará (grant 09100085–8). S.A.R.P. and C.M.G.D.F. were supported by a fellowship from the Coordenação de Aperfeiçoamento de Nível Superior (CAPES).

## DECLARATION OF INTEREST

None.

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