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Clinical conditions and risk factors, in predicting risk of *Respiratory Syncytial Virus* (RSV)-ALRTIs in children

Abstract

Background: Acute Lower Respiratory Tract Infections (ALRTIs) are an important cause of morbidity and mortality in infant and young children in Africa. The World Health Organization (WHO) in 2015 reported that about four million children aged less than five years die annually and 1.9 million of these deaths result from complications of ALRTIs, mainly pneumonia. This study therefore aims to investigate prevalence of *Respiratory Syncytial Virus* (RSV) infection and the associated risk factors of ALRTI among under-five children in Lagos, South-West Nigeria.

Methods: This is a cross-sectional study among 200 children in Lagos, South-West Nigeria, with *Respiratory Syncytial Virus* (RSV) infection using Reverse transcription PCR (RT-PCR). A structured questionnaire was self-administered to collect attributes that might directly or indirectly associate with the risks of acquisition of RSV infection. Data was analyzed by both descriptive and inferential statistics using SPSS.

Results: A total of 200 participants were recruited, *Respiratory Syncytial Virus* (RSV) infection was detected in Forty-five (22.5%) using Reverse transcription PCR (RT-PCR). Acute lower respiration tract infections (ALRTIs) were most predominant in age group 25-60 months (35%). One hundred eight (64%) had pneumonia while 72 (36%) had bronchiolitis. Furthermore, exclusive breastfeeding, family history of atopy, history of nasal instrumentation and attended creche were significant risk factors for RSV-ALRTIs.

Conclusion: Infants with a family history of atopy are at increased risk of severe RSV infection, and longer hospital stay. Also, there was a significant association between RSV infection and History of nasal instrumentation as well as not been exclusively breastfed.

Keywords: respiratory tract infection; *respiratory syncytial virus*; bronchiolitis; pneumonia.

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Abbreviations: ALRTIs, acute lower respiratory tract infections; ALDS, acute lung distress syndrome; cDNA, copy deoxyribonucleic acid; HIV, *human immunodeficiency virus*; LASUTH, lagos State university teaching hospital; LREC, health research and ethics committee of the lagos state; RNAse, ribonucleases; RSV, *respiratory syncytial virus*; RT-PCR, reverse transcription-polymerase chain reaction; SDG, sustainable development goal; SPSS, software statistical package for social sciences; WHO, world health organization

Introduction

Respiratory tract infections remain the foremost cause of death in young children[1] and may be a major obstacle to achievement of Sustainable Development Goal (SDG) 3, which is to ensure good health and well-being for all.[2] *Respiratory Syncytial Virus* (RSV) is however the leading cause of viral acute lower respiratory-tract infections accounting for between 15%-45% of all cases of ALRTI.[3] In Nigeria, the largest country in sub-Sahara Africa with high rate of under-five mortality of which 20% is due to ALRTI has paucity of data on the viral etiology of ALRTI.[4] On this basis, it is highly important to investigate the prevalence of RSV in ALRTIs in this region, to also determine the age specific prevalence of RSV, assess the severity of acute respiratory infections due to RSV and document the risk factors associated with RSV-ALRTI.[5]

Respiratory Syncytial Virus primary infections are almost always symptomatic but may vary from a mild common cold to a life threatening lower respiratory tract infections.[6] Most infants show signs of improvement within 3 or 4 days after the onset of lower respiratory tract disease. Typically, the infant present with fever, cough, tachypnea, cyanosis, retractions, wheezing, and rales. Studies show that children at risk of developing severe RSV infections are likely to also have genetic traits that are commonly found in children with other chronic respiratory diseases. These groups include the following: immune-compromised babies, babies with congenital heart disease and underlying lung diseases.[7]

A large percentage of children with RSV who develop acute lung distress syndrome (ALDS) recover with no difficulty, for those who progress in management is largely supportive.[8] Almost all children with RSV have low oxygen levels and oxygen is needed for hospitalization. A drug called ribavirin is used to treat RSV by increasing the body's immunity to the virus.[9] For this treatment, patients may take the drug for 12 hours or more each day, for 3-5 days. Ribavirin is not associated with any significant toxicity. The viral resistance to ribavirin has not been documented.[10] Other treatments for the virus may include bronchodilators (alpha and beta adrenergic agents), corticosteroids, airway clearance and antiviral drugs.[11]

A significant proportion of children with RSV ALRTI recover without difficulty, for those who do progress, management is largely supportive. Almost all children with RSV have low oxygen levels and oxygen is needed for hospitalization. An antiviral agent ribavirin, has been recommended for specific treatment of RSV infection[9] The drug may be administered this way for twelve or more hours per day for 3 to 5 days. Furthermore, ribavirin aerosol has not been found to be associated with any significant toxicity. Viral resistance to ribavirin has not been documented. Other supportive therapy includes use of bronchodilators (alpha and beta adrenergic agents), corticosteroids, antiviral, and airway clearance.[9]

This study aims to investigate the prevalence of *Respiratory Syncytial Virus* (RSV) infection and associated risks of ALRTI among under-five children in Lagos, South-West Nigeria. This will enable us to have data on the associated risks in ALTRI-RVS, make evidence-based recommendations on the need for childhood vaccination, reduce the financial burden of hospitalization and antibiotic use in childhood ALRTI and ultimately help to reduce childhood mortality from ALRTI.

Aims: To determine the molecular prevalence of *Respiratory Syncytial Virus* (RSV) infection, and evaluate the associated risk factors of ALRTI among under-five children in Lagos, South-West Nigeria.

Methods

Study design and location

This was a cross-sectional study conducted among children under the age of five years who were admitted to the Paediatric unit of Lagos state University Teaching Hospital in Nigeria. It was designed to determine the factors that could contribute to ALRTIs. Lagos State University Teaching Hospital is the most accessible tertiary and referral medical facility in Lagos State, and it sees more than 4 million people annually. The hospital has 350 beds, and the pediatric department has 98 beds.

Study population

The study population comprise of under-five children admitted to the Paediatric unit of Lagos State University Teaching Hospital with ALRTI.[12] ALRTI were determined based on a medical diagnosis of bronchiolitis or pneumonia and based on the presence of symptoms such as cough, coryza, rhinorrhea, fever, or retractions.[13]

Sample size determination

The sample size was determined by using single population proportion formula considering prevalence of lower respiratory tract infection as 31% from previous study in Africa children,[12] margin of error as 0.05 and 95% as confidence interval. After including 10% non-response rate, 200 under-five years' children were recruited into this study.

Laboratory procedures

Specimen collection

Two hundred study participants was recruited, and nasopharyngeal swab was collected within 24 hours of hospital admission using Nasopharyngeal flocked swab.[14] The swab was gently inserted up the nostril towards the pharynx until resistance is felt and then rotated 3 times to obtain epithelial cells, then withdrawn and put into1ml of transzol reagent in a 1.5mls RNAse free safe lock micro centrifuge tubes.[15] The Specimens was transported on ice pack to the Medical Research Laboratory of LASUTH within one hour of collection, sample were vortexed and transferred into another 1.5mls safe lock micro centrifuge tubes using a micropipette and subsequently stored at -70^{0}C in batches before RNA extraction.

RNA extraction

Each sample was brought to room temperature for a few minutes to thaw, then vortexed to homogenize and decanted the supernatant. Aspirate two hundred (200) µL of chloroform into the sample and centrifuge at 10,000xg for 15 minutes at 40°C. Aspirate the supernatant into a new RNase-free Eppendorf tube. Add five hundred (500) µL of isopropanol to the tube and incubate at room temperature for 10 minutes. The sample was centrifuged at 10,000 xg for 10 minutes at 40°C, and then the supernatant was decanted. 1ml of 75% ethanol was added to the pellet and vortexed for 5 minutes, then the sample was centrifuged at 7,500xg for 5 minutes at 40°C. Discard the supernatant and air-dry the precipitate (RNA precipitation). Add one hundred (100) µL of dissolving solution to the RNA pellet and incubate at 600°C for 10 minutes. Then store it at –700°C for PCR processing.

DNA amplification using reverse transcription PCR (RT-PCR)

In order to generate a representative cDNA pool from the RNA template, mix the following materials in a single tube to make the total volume 20 µl. The content of the tube is mix gently and incubate at 42°C for 50 minutes to synthesize the first-strand cDNA. Then, the reaction was inactivated by incubating the mixture at 70°C for 10 minutes, and 180 µl of RNase-free water was added to dilute the resulting cDNA. These samples are used in PCR reactions. The polymerase chain reaction was performed an automatic thermocycler (Biometra) programmed.

Gene detection using agarose gel electrophoresis

From the negative control, sample, and ladder mixture, place twenty (20) µl each on a 2% agarose gel (2% w/v in 1x TAE buffer) and run at 100V in 1x TAE buffer 45 minutes. The bands were visualized under the gel documentation system (BioRad Gel Doc-XR, USA) and screen shots were captured. Compare the size of the separated bands (DNA fragments) with the Gene Ruler TM 100bp+ DNA ladder (MBI Fermentas, Life Sciences, Canada).[16]

Ethics approval and consent to participate

Ethical approval was obtained from Health Research and Ethics Committee of the Lagos State University Teaching Hospital, Reference No- LREC.06/10/890. A written informed consent was also obtained from the parent/ caregivers of the study participants. The informed consent form contained the following information: names and affiliation of investigator, a plain language description of the study, the duration of the study, the right to withdraw at any time, the ethics committee approval and the privacy guarantee.

Data collection

Structured interviewer-administered questionnaire which has two sections was used. Section 1 was designed to collect socio-demographic data of participants (age, sex, birth etc), and clinical conditions such as bronchiolitis and pneumonia, while section 2 consist of attributes that might directly or indirectly put them at risks for the acquisition of RSV infection such as history of congenital heart disease, nasal instrumentation, and family history of atopy among others.

Data analysis

Data collected from each participant was subjected to descriptive and inferential statistical analysis using the software statistical package for social sciences (SPSS) version 20. Results are presented in tables and charts. Statistical significance between variables was determined using chi-square and level of significance was considered at $P < 0.05$.

Result

Age and clinical diagnosis distribution of ALRTI among participants

Two hundred (200) participants were recruited in this study having satisfied the inclusion criteria. The mean age for participant was 21.56±19.95. Acute lower respiration tract infections (ALRTIs)

were most predominant in age group 25-60 months (35%) followed by age group 13-24 months (27%) and the least was recorded in age group <2 month (4.5%). Furthermore, the clinical presentation of the participants shows 128(64%) had pneumonia while 72(36%) had bronchiolitis. As shown in the Table 1.

Table 1 Distribution of ALRTI subject according to clinical diagnosis

Age Month	Pneumonia (128) n (%)	Bronchiolitis (72) n (%)
<2 month	6(4.7)	3(4.2)
6-Feb	25(19.5)	12(16.7)
12-Jul	20(15.6)	10(13.8)
13-24	36(28.2)	18(25)
25-60	41(32)	29(40.3)
Total	128	72

Risk factors associated with ALRT-RSV infection

Among the 45 participants who were positive for RSV, 33 (73.3%) attended crèche and this was found to be statistically significant (p= 0.04). Furthermore, a significant association was observe among exclusively breastfed children (p=0.010), those with history of nasal instrumentation (p=0.002) and family history of atopy (p=0.030). However, those with history of hospital admission, congenital heart disease and HIV infection were not statistically significant to RSV-ALRTI acquisition. Table 2 further illustrates this.

Table 2 Risk factors associated with ALRT-RSV infection

Risk Factor	RSV Negative n (%)	RSV Positive n (%)	X2	P value
1. Gender			1.14	0.286
· Female	52 (33.5%)	19 (42.2%)		
· Male	103 (66.55%)	26 (57.8%)		
2. Smokers in the House			0.029	1
· No	149 (96.1%)	43 (95.6%)		
· Yes	6 (3.9%)	2(4.4%)		
3. Crèche Attendance			4.907	0.04
· No	70 (45.2%)	12 (26.7%)		
· Yes	85 (54.8%)	33 (73.3%)		
4. Exclusive Breastfeeding			7.608	0.01
· No	54 (34.8%)	26 (57.8%)		
· Yes	101 (65.2%)	19 (42.2%)		
5. Nasal Instrumentation			8.792	0.002
· No	107 (69%)	41 (91.1%)		
· Yes	48 (31.0%)	4 (8.9%)		
6. Previous Hospital Admission			0.005	1
· No	87 (56.1%)	25 (55.6%)		
· Yes	68 (43.9%)	20 (44.4%)		
7. Family History of Atopy			5.049	0.031
· No	127 (81.9%)	43 (95.6%)		
· Yes	28 (18.1%)	2 (4.4%)		
8. Congenital Heart Disease			0.079	1
· Absent	139 (89.7%)	41 (91.1%)		
· Present	16 (10.3%)	4 (8.9%)		
9. HIV Infection			1.477	0.577
· Absent	151 (92.4%)	45 (100.0%)		
· Present	4 (2.6%)	0 (0.0%)		
10. Chronic Lung Disease				
· Absent	149 (96.1%)	45 (100%)	1.787	0.341
· Present	6 (3.9%)	0 (0.0%)		

Discussion

This study is a cross-sectional study of *Respiratory Syncytial Virus* in children in Lagos, southwestern Nigeria. This study analyzed selected risk factors for acquiring RSV infection previously reported by several studies. This includes gender, parental smoking, previous hospitalization history, congenital heart disease, and HIV infection.[17] However, no significant associations were found between these variables and RSV infection. It was found that the history of nasal devices, atopic family history, and non-exclusive breastfeeding were significantly associated with RSV infection. Similarly, a significant association was found between crèche attendance and RSV infection. Several studies have reported an association between RSV infection and crèche attendance.[17,18]

The reason alluded to this is due to close interaction among children in creche. This interaction increases the risk of infection transmission, especially respiratory infections. Regarding breastfeeding, the study found that children who were not exclusively breastfed had a 25% increased risk of RSV infection. This finding is inconsistent with research done in Ilorin and Benin.[19,20] However, some other studies are consistent with the findings of this study on the association between non-exclusive breastfeeding and RSV infection. Studies conducted in India, Kenya, and Mexico report that children who are not exclusively breastfed have an increased risk of RSV infection by 25%-45%. [21,22]

This study found that children with a family history of atopy had a 25% likelihood of having RSV infections. A study conducted in Ghana among hospitalized infants with ALRTIs reported a 45% risk of RSV infection in children with family history of atopy.[23] This is corroborated by a study, which concluded that infants with a family history of atopy are at increased risk for severe RSV infection as indicated by higher rates of hospitalization, longer hospital stay, and more frequent occurrence of bronchiolitis leading to asthma in later years.[24] In contrast to this is a long term prospective study in children with RSV infection. The study reported no significant association between family history of atopy and acquisition of RSV- ALRTIs.[25]

Chronic lung disease and HIV infection are documental risk factors for RSV-ALRTIs in various studies.[26] However, findings from this study showed that these risk factors were not statistically significant. This is likely due to the few numbers of children with these

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anomalies recruited into this study. The study reported that there was no significant association between a family history of atopy and the acquisition of RSV-ALRTIs.[25] In various studies, chronic lung disease and HIV infection are documented risk factors for RSV-ALRTIs.[26] However, the results of the study indicate that these risk factors are not statistically significant. This is likely due to the few numbers of children with these anomalies recruited into this study.

Limitations

This study would have been more robust with more cases and the inclusion of additional clinical and laboratory data.

Conclusion

The study reveals that crèche attendance, family history of atopy, previous nasal instrumentation and not being exclusively breastfed were found to have significant association with RSV-ALRTI.

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Conflicts of interest

There are no conflicts of interest.

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