Title: Respiratory Syncytial Virus-Related Severe Acute Lower Respiratory Tract Infection Among Under-Fives at a Public Tertiary Hospital in Northwestern Nigeria: Epidemiology and Seasonality.

Running title: RSV-ALRTI among hospitalized under5s in Nigerian

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Abstract:

Background- Globally, 33 million cases of Respiratory Syncytial Virus (RSV) infections occur annually among under-fives. Ninety-nine percent of deaths from RSV occur in low- and middle-income countries. Under-five pneumonia mortality in Nigeria was estimated at 140,520 in 2017, but RSV epidemiological data is scant due to poor awareness and limited testing. Vaccines for RSV are currently under development and RSV mortality data from this high-mortality low resource setting are essential to maximizing the potential benefit of vaccination as well as promoting vaccine uptake. This study aimed to describe the epidemiology and seasonality of RSV-ALRTI in children younger than 5 years in Zaria, Northwestern Nigeria.

Methods-A prospective cohort study was conducted among children aged 1 month to 5 years who were hospitalized with acute lower respiratory tract infection (ALRTI) in the Emergency Pediatric Unit of Ahmadu Bello University Teaching Hospital from November 2018 to November 2019. Naso-pharyngeal swabs were obtained for RSV testing using a point-of-care immunoassay technique.

Results- Thirty-three percent (35/106) of the children had RSV-related ALRTI. The median age of RSV-positive cases was 8 months (IQR 3-14). Two-thirds of children (68.6%, 24/35) were below 12 months. The RSV mortality rate was 5.7% (2/35). RSV occurred in 10 months of the year with peaks in March and July.

conclusions- A third of admitted children with ALRTI were positive for RSV. RSV significantly contributes to childhood pneumonia and testing will raise awareness of this important pathogen. The dual seasonal peak observed in our study may have implications for vaccine implementation.

(WC-250)

Keywords: Respiratory syncytial virus-related acute lower respiratory tract infection (RSV-ALRTI), Under-fives, Epidemiology, Tertiary hospital, Northwestern Nigeria.

Data availability statement- This is available on demand

Conflicts of Interest:

BL- Has regular interaction with pharmaceutical and other industrial partners. He has not received personal fees or other personal benefits. UMCU has received major funding (>€100,000 per industrial partner) for investigator-initiated studies from AbbVie, MedImmune, Janssen, Pfizer, the Bill and Melinda Gates Foundation, and MeMed Diagnostics. UMCU has received major cash or in-kind funding as part of the public-private partnership IMI-funded RESCEU project from GSK, Novavax, Janssen, AstraZeneca, Pfizer, and Sanofi. UMCU has received major funding from Julius Clinical for participating in the INFORM study

NM -UMCU has received fees for consulting from Merck, Abvie

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Ethics approval was obtained from the Human Research and Ethical Committee (HREC) of the Ahmadu Bello University Teaching Hospital, (ABUTHZ/HREC/E22/2018).

Permission to produce material from other sources- Not applicable

Consent - Written and informed consent was obtained from the parents or caregivers of the subjects.

**INTRODUCTION**

Respiratory syncytial virus (RSV) is a significant cause of acute lower respiratory infections (ALRTI) in children below 5 years of age, 1 as well as an important cause of hospitalizations and childhood mortality. RSV causes both upper respiratory tract infections (URTI) as well as lower respiratory tract infection (LRTI), namely, bronchiolitis and pneumonia.2 Non-respiratory manifestations of RSV involving the cardiovascular system and central nervous system have also been reported.3

Globally, the incidence of Respiratory Syncytial Virus related- Acute Lower Respiratory Tract Infection (RSV-ALRTI) is estimated at over 33 million cases each year with approximately 10% resulting in hospitalization.1, 2, 4 It is estimated that between 94,000 and 149,400 RSV-associated deaths occur annually,4 and 99% of these deaths occur in low and middle-income countries (LMIC).1,4,5

Nigeria had the world’s 5th highest pneumonia-related child mortality rate in 2017 with 140,520 deaths.6 Pneumonia accounts for 19% of total childhood mortality in Nigeria. Whereas bacterial pneumonia deaths are largely expected to decrease with widespread acceptance and use of preventive *Haemophilus influenza b* and pneumococcal vaccines, it is foreseen that viruses, including RSV, will gain more prominence as a cause of Lower Respiratory Tract Infection (LRTI).4, 7 The role of viruses in the etiology of LRTI especially in LMIC is often underrated as most LRTI are generally assumed to be of bacterial origin, and treated with antibiotics. This assumption results in antibiotic over-use which has led to the emergence of multidrug-resistant organisms. Microbiologic testing is rarely performed due to a lack of appropriate resources, thus, the impact of viral respiratory infections on childhood morbidity and mortality is unclear. Nevertheless, it was estimated that Nigeria, India, China, Pakistan, and Indonesia, accounting for 43% of the global under-5 population, contributed to approximately half the world’s RSV-ALRTI burden in 2016.4

Prevalence rates for RSV infections among Nigerian children younger than 5 years range from 17% to 36%.8-11 However, it is known that even within the same country, the epidemiology and seasonality of RSV vary.12 There has been no study reported from Northwestern Nigeria.

RSV vaccines and monoclonal antibodies are currently in late-phase clinical trials.13 The benefit of a vaccine in any population of introduction will depend on a robust description of its epidemiology including seasonality to derive maximum gains. We aimed to describe the epidemiology and seasonality of RSV- related ALRI among hospitalized children below the age of 5 years. A better understanding of RSV epidemiology may inform routine testing, improve awareness especially among healthcare workers, and improve vaccine promotion and uptake when they become available.

**MATERIALS & METHODS**

This was a prospective hospital-based cross-sectional study conducted from November 2018 to November 2019. Children aged between 1 and 59 months admitted into the Emergency Pediatric Unit (EPU) of the Ahmadu Bello University Teaching Hospital (ABUTH), with features of severe ALRTI were consecutively recruited. ABUTH is a referral centre for secondary health facilities within the region, with a catchment area of 216, 065 Sq. km (which is 25.75% of Nigeria's total landmass)

Severe ALRTI was defined as acute cough and/or difficulty in breathing characterized by lower chest wall in-drawing with or without fast breathing for age and with or without cyanosis. Neonates (defined as children younger than 28 days) and cases of suspected foreign body aspiration were excluded.

A detailed history, physical examination, and laboratory findings were documented in an interviewer-administered validated questionnaire.14 Data on climatic conditions and average environmental temperature and humidity from November 2018 to November 2019 was obtained from the Nigerian meteorological agency.

**Specimen collection and Processing**

Rapid qualitative detection of RSV antigen (viral fusion protein) from nasopharyngeal samples from each patient was performed using a dipstick immuno-assay (QuickVue ® RSV by Quidel, San Diego, CA 92121USA USA). QuickVue RSV has a sensitivity of 90%, a specificity of 98.8% respectively, a negative predictive value of 94.6%, and a positive predictive value of 99.3%. 15

The patients’ nasopharyngeal samples were obtained according to the manufacturer’s instructions. Samples were taken no later than 48 hours after admission by trained health care staff. Quality control was included according to manufacturers’ instructions and invalid tests were repeated. Where delay before testing was anticipated, the sample was stored at 2°C to 30°C, in a clean, dry, closed container and tested within 8 hours after allowing it to come to room temperature.

**Statistical analysis**

Using WHO child growth standards, we calculated Z scores for weight for age, height for age, and weight for height. The monthly number of ALRTI admissions, RSV cases, humidity and mean temperature were also plotted.

We used descriptive statistics to calculate all the variables (SPSS version 23.0). Mann-Whitney U test was used for statistical comparison of RSV infected and RSV uninfected groups. Correlation analyses were used to determine the relationship between monthly RSV cases and continuous variables (monthly ALRI admissions, temperature, and humidity). A *p*-value of <0.05 was considered significant.

**Ethics**

The protocol was approved by the Human Research and Ethical Committee (HREC) of the Ahmadu Bello University Teaching Hospital, (ABUTHZ/HREC/E22/2018). Written and informed consent was obtained from the parents and caregivers.

**RESULTS**

Of the 140 eligible children, only 106 were enrolled in the study (75.7%). Figure 1 shows the patient flow chart. The median age of the subjects was 10 months (IQR 4 -18 months). A third of the study subjects (32.1%) were aged 1-6 months. Thirty-five of the 106 enrolled children (33.0%) tested positive for RSV.

**Socio-demographic characteristics of subjects with RSV-ALRI**

Two-thirds of the RSV-positive cases were infants (See Fig 2). The median age of the subjects was 8 months (IQR 3-14 months). RSV positive cases were younger (8 months, IQR 3 – 14 months) compared to the RSV negative cases (10 months, IQR 6 - 18 months) but this difference was not statistically significant *p* = 0.525).

The median age of the mothers was 29 years (IQR 24 – 36 years). The majority (68.3%) had at least a secondary school education. However, 25% (16/35) of the mothers were not gainfully employed or were earning below the national minimum wage of N18,000 ($60) per month. For 65% (23/35) of children with RSV, this was their first hospitalization. Twenty-eight percent (10/35) had no siblings and only 11.4% attended any form of daycare. The exclusive breastfeeding rate in the first 6 months of life was 28.6%. The majority were predominantly breastfed (breast milk and water). In all, over 80% were breastfed for more than 6 months.

**Seasonality of RSV**

RSV was detected in 10 months of the year (see Fig 2). There were no cases in May and October. Two peaks were identified; a smaller peak in March, (which coincided with the period just before the onset of the rainy season), and a higher peak in July. Humidity was weakly correlated with the frequency of RSV (r = 0.66, *p* = 0.838). Although most RSV cases occurred when the environmental temperature was between 23ºC and 26ºC, there was no correlation between the number of RSV cases and average environmental temperature (r = -0.312, *p* = 0.323).

**Risk factors for RSV**

Risk factors for RSV

The proportion of premature subjects in the RSV infected group was twice as high as the uninfected group, but this was not statistically significant. There were also no statistically significant differences between RSV infected and uninfected children concerning age, sex, parental smoking, exposure to bio-fumes, or the number of siblings in the household (Table 1). Five (14.3%) children in the RSV infected group had congenital heart disease in comparison to 4 (1.4%) in the uninfected group (p=0.439). Four (11.4%) subjects had co-infections with vaccine-preventable pathogens i. e. measles (2), tuberculosis (1), and pertussis (1). There was no statistically significant difference with regards to the above when RSV positive and negative groups were compared. The mortality rate in the RSV-positive group was 5.7% (2/35). Both children were aged 4 months, one of whom had a ventricular septal defect.

**DISCUSSION**

This study showed that a third of the hospitalized children with severe ALRTI tested positive for RSV. This prevalence is similar to what has been previously reported by Robertson *et al* (35%), Johnson *et al* (30.4%), and Oladele et al (34.2%) in South-western Nigeria, 9, 11, 12 but lower than the 60.4 % reported by Obodai et al in Accra, Ghana.10 It is however higher than the average global prevalence of 22% reported by Shi and Yassine et al 24.4% in the Middle East and North African region.4, 16

Younger age below 6 months is a well-described risk factor for RSV. 4, 14, 10, 17, This was observed in our study as two-fifths of children with severe RSV-ALRTI were below 6 months. The predisposition of the very young to RSV is related to an immature innate viral immunity and the fact that passively-derived maternal RSV antibodies usually decline by 6 months of age.17 It has also been postulated that the relatively higher figures noted in some regions may be related to the social practice of sheltering of infants for the first 40 days of life as well as the presence of large family sizes, 12 factors which are both prevalent in the area of our study. This susceptibility of infants highlights the importance of implementing preventive measures, specifically, vaccination for this age category. RSV was less common in older age groups, likely due to decreased susceptibility for severe RSV infection as a result of acquired immunity over time.17 The authors strongly believe that prematurity is also a risk factor in Nigeria, considering the high proportion of RSV positivity rate among infants born prematurely in this study.

The traditional infant feeding practice in Zaria and its surrounding region is to give breast milk and water for 18-20 months even though the World Health Organization (WHO) recommends exclusive breastfeeding for the first six months and continued breastfeeding for two years and beyond.18 Breastmilk contains immunoglobulins, lactoferrin, lymphocytes, and several immunomodulatory factors which promote protection from RSV as well as other diseases.18, 19 According to Pandolfi et al, the duration of protection directly correlates to the duration of breastfeeding. 20 The promotion of exclusive and extended breastfeeding is thus, beneficial in the prevention of RSV infection in infants. Malnutrition is a well-known cause of immunodeficiency and is associated with increased severity of diseases, but this risk seems to be low for RSV.21

It is pertinent to note that in the typical African setting, families tend to live in closely-knit communities with child care being the responsibility of relatives and neighbors.22 Where this is not available for a working mother, the child is left with a provider, usually in her (provider's) home who often has many more children to care for. This type of arrangement is also termed 'daycare' or 'gidan rayno' apart from the more formal or structured daycare. No categorical distinction was made with regards to the daycare type used in this study. In future studies, it may be worthwhile to elaborate this further with more detailed clinical data on household setup and adapt the definition of daycare to the local setting.

Meteorological factors such as temperature and rainfall as well as geography are important predictors of RSV epidemics.23, 24 Obando- Pacheco *et al*,25. in a meta-analysis providing a global overview of the seasonality of RSV, showed that RSV season occurs in spring in the southern hemisphere and winter in the northern hemisphere. In equatorial regions, however, no clear pattern has been observed with RSV infection. Infections occur almost year-round. 12,25,26,27 This is in agreement with our findings where RSV cases were observed in 10 months of the year. In warmer climes closer to the equator, increased humidity at stable temperatures allows RSV particles to survive in aerosols by preventing them from desiccation and losing infectivity and thereby sustaining infections almost all year-round.2 In this study, the greatest activity was observed in July when the rainy season was at its peak and the average humidity was 76%. Human behavior impacts significantly on the predominance of viruses in the wet season in the tropics. This is due to forced indoor stay which contributes to overcrowding thereby enabling increased transmission. 9,10,25,28,29 In this study, there was also a small surge of cases during the hot and dry months of March. This small peak has also been reported by Robertson *et al* who conducted a study in Ibadan, Southwestern Nigeria.12

The strength of this study lies in the wide catchment area which the hospital serves. However, it is subject to several limitations. It is a single-center and single-season study, and findings cannot be extrapolated to the rest of the country as Nigeria has a large landmass with differing regional climatic conditions. The reliance on a single laboratory test for detecting the antigen could have likely underestimated the disease burden due to its lower sensitivity compared to other methods. Our focus was on a single pathogen and as such, we may have missed the relative importance of other respiratory pathogens. Additionally, thirteen cases were missed by the study staff due to weekend or late-night arrival to the facility. Our small sample size restricted our ability to undertake subgroup analysis to analyze for risk factors.

This study contributes to local data on RSV epidemiology which will be required for policy development and implementation by the government and other stakeholders. The data provided support the need for RSV routine testing, surveillance, and awareness creation.

In conclusion,a third of children admitted with ALRTI were positive for RSV, with the majority younger than 12 months of age. RSV occurred in 10 months of the year and significantly contributed to childhood pneumonia. The dual seasonal peaks observed in our study may have implications for the introduction of RSV immunization strategies.

RSV should be considered a high priority for public health and routine RSV testing should be implemented in health care settings in LMICs to increase the knowledge and awareness of RSV-associated childhood disease burden. This will decrease antibiotic usage and the emergence of multidrug-resistant organisms, as well as encourage the uptake of RSV vaccines when they become available.

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Figure legends:

1. Figure 1: Patient flow chart
2. Figure 2: Seasonality of RSV
3. Figure 3: Seasonality of RSV in Zaria