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Epidemiology and genetic diversity of respiratory syncytial virus in adults 50 years and older with acute respiratory infections in Accra, Ghana

Comfort Nuamah Antwi[1,2], Bartholomew Dzudzor[2], James Odame Aboagye[1,3], Vishnu Nene Limon Abayateye[4], Joseph Ahia Quarcoo[1], Asantewa Sisi Yaa Anang[1], Gloria Gifty Whyte[3], John Kofi Odoom[1] and Evangeline Obodai[1*]

Abstract

Background Human respiratory syncytial virus (RSV) is responsible for lower respiratory tract infections, particularly posing a significant threat to infants, the elderly, and immunocompromised individuals. However, the disease burden is poorly understood in the adult population in Africa. This molecular study investigated the occurrence of RSV in adults 50 years and older and assessed the genetic variability of circulating RSV genotypes in patients with acute respiratory tract infection (ARI) in Accra, Ghana.

Methods From March to October 2023, patients who are ≥ 50 years of age with confirmed ARI cases were enrolled from three hospitals in Accra, Ghana. Nasopharyngeal specimens were collected and analyzed for RSV using real-time quantitative PCR. The second hypervariable region of RSV-positive samples was targeted for sequencing. Bioinformatics analysis was carried out to identify the predominant circulating genotypes and a phylogeny established between sequences from this study and other globally circulating RSV genotypes. Amino acids deduction analysis was performed to identify the genetic variability and evolution of the RSV genotypes identified.

Results A total of 212 patients were enrolled. RSV infection was confirmed in 11 (5.2%) participants. RSV infection was more prevalent among patients aged 65 years and older (8/11, 54.5%). Patients with underlying chronic diseases (18%) suffered severe medically attended RSV complications requiring intensive care and ventilation support. RSV disease was significantly associated with cough ($p=0.023$). Phylogenetic and amino acid sequence analysis revealed RSV-B sequences clustered as BA; specifically, the globally prevailing BA9 genotype. No cases of RSV-A were identified. RSV/BA9 dominated the season from July to October 2023. Specific amino acid substitutions both outside and within the duplication region of the G gene were present, and presence of individual clusters and branches provided evidence of strains diversification and evolution.

Conclusion This study provides the first baseline report of RSV disease occurrence among adults ≥ 50 years in Ghana. It reveals the genetic diversification of prevailing RSV/BA9 genotypes identified and addresses the need for continuous RSV surveillances and targeted interventions in this frail population.

Keywords Respiratory syncytial virus, Acute respiratory infection, Older adults, Molecular studies, Ghana

*Correspondence:
Evangeline Obodai
eobodai@noguchi.ug.edu.gh
Full list of author information is available at the end of the article

Background

The human respiratory syncytial virus (RSV) is primarily responsible for lower respiratory tract infections, particularly posing a significant threat to infants, the elderly and immunocompromised individuals [1, 2]. Despite being commonly known as a pediatric disease, 78% to 82% of all RSV associated deaths occur in persons ≥ 65 years of age [3, 4]. Most RSV infections in older adults present mild cold-like symptoms, such as a runny nose, sore throat, cough, malaise, fever, and headache [5]. However, in some cases, adults may develop pneumonia and bronchitis, leading to severe illness that necessitates hospitalization [6]. In recent reports by the United States Center for Disease Control and Prevention (U.S. CDC) in 2023, RSV was responsible for annual hospitalizations rates of 60,000–120,000 and 6,000–10,000 deaths among individuals ≥ 65 years of age. As one gets older, the gradual deterioration of the immune system, decreased strength of the respiratory muscles and diaphragm and the decreased protective mucus levels, lung compliance and elastin increase their risk of severe respiratory complications including RSV illnesses [7]. Moreover, adults ≥ 65 years of age who have conditions like asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), weakened immune systems, and residents of long-term care facilities face elevated risk of experiencing medically attended RSV infections and hospitalization rates than younger adults who are 18–49 years of age [8]. RSV incidence exhibits seasonal distribution patterns and annual epidemics peak during the winter months in the temperate regions, whereas in the tropical and subtropical locations the RSV peaks are seen during the rainy season [9, 10].

RSV was first differentiated into two antigenic groups: RSV-A and RSV-B using monoclonal antibodies [11]. A comprehensive understanding of RSV-A and RSV-B into several genotypes has been made possible by sequencing the second hypervariable region (VR2) of the G glycoprotein [12]. Seasonal outbreaks over the past 20 years have depicted high rates of positive selections and duplication events in the RSV G glycoprotein. A current RSV-B genotype (BA) that was first identified in Buenos Aires, Argentina in 1999, has spread worldwide and replaced the previously described RSV-B genotypes [13]. BA genotype has differentiated into 14 sub-genotypes BA1-BA14, [14–17] and are characterized by 60-nucleotide duplication in the VR2 of the G gene [13]. A novel ON1 on the other hand, with 72-nucleotide duplication that emerged from Canada during the 2010/2011 winter season, has since been reported to spread worldwide and dominated RSV-A genotypes [16, 18]. To date, 13 RSV-A and 19 RSV-B genotypes have been reported from different geographical locations [12, 14–17, 19–21]. It is established that strain variation contributes to the ability of RSV to cause frequent reinfections [22], which occur throughout life extending into old age [8].

Despite the increasing knowledge of RSV as an etiology of severe acute respiratory tract infections among older individuals in developed countries, limited data exist for RSV disease among older adults in Africa. Over 95% of hospitalizations and deaths related to RSV have been reported to occur in low- and middle-income countries (LMICs), however these reports were based mostly on studies in children. [23] In Ghana, for the few molecular studies that exist on RSV children, the prevalence is quite higher in infants less than one year of age than those between the ages of one and three and the viral activity was observed from June to December [24–26]. It is important to note that the source of RSV infections in older adults are primarily through direct contact with their grandchildren, other community dwelling children or staff from nursing care homes [27].

The recent introduction of RSV vaccine recommended by the US. CDC for adults ≥ 75 years and those 60–74 years of age with increased risk of severe RSV infections has paved way for many clinical trial studies in the developed countries.[28]. However, the WHO's Strategic Advisory Group of experts on immunization identified the lack of age-specific estimates for disease burden and mortality data on RSV in African and South Asia communities as significant gaps that impede recommending the introduction of RSV vaccine in lower- and middle-income countries (LMICs) [29]. This current study therefore investigated the occurrence of RSV in both hospitalized and non-hospitalized adults aged ≥ 50 years old with acute respiratory tract infection (ARI) and assessed the monthly circulation pattern of RSV. It also highlighted the genetic diversity among RSV strains identified, providing baseline information on molecular surveillance and the need for future introduction of RSV therapeutics in Ghana.

Materials and methods

Study design

This was a cross-sectional study carried out among patients who were 50 years and older with ARI who visited any of the three designated hospitals in the Greater Accra region of Ghana to seek medical assistance from April to October 2023. Patients who met the case definition for ARI were selected by the nurses and recruited into this study. ARI was defined as cough, presumed pneumonia, breathing faster than usual with short or quick breaths with difficulty breathing; in addition to running nose, sore throat, wheezing or apnea [30]. Research assistants collected their patient demographic information after they consented to participation in the

study. In addition, clinical symptoms and other relevant information of both hospitalized and non-hospitalized participants were collected by using a structure questionnaire (Supplementary sheet 1).

Study sites and participants

The study was conducted in three hospitals in Ghana. These hospitals were the University of Ghana hospital Legon (UGHL); which provides primary and secondary healthcare to the university community and its environs, Korle-Bu Teaching Hospital (KBTH); which is a leading teaching and referral hospital, providing tertiary healthcare services to Ghanaians across the country, and the University of Ghana Medical Centre (UGMC); a quaternary healthcare institution. Patients who presented with ARI to the hospitals were eligible for inclusion as study participants if they were at least 50 years of age.

Sample collection

From March to October 2023, nasopharyngeal and/or oropharyngeal swab specimens were collected from patients with informed consent. The specimens were collected within 1–5 days of onset of ARI. These specimens were placed in 3 ml of viral transport media in primary containers, kept on ice and transported immediately to the Department of Virology, Noguchi Memorial Institute for Medical Research, University of Ghana for wet lab analysis.

RNA extraction and RSV subtyping

Upon receipt in the lab, specimens were vortexed and aliquoted into 2 mL cryovials. Total ribonucleic acid (RNA) was extracted from 140 µL of the specimen using the QIAmp Viral RNA Mini kit (QIAGEN, Germany) following the manufacturer's protocol. The remaining aliquots were stored at −80°C as backup for additional analysis. For the molecular detection, reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) was used to amplify the N gene for the human RSV. The extracted RNA (5 µL) was amplified in a 20 µL of reaction mixture containing RSV primers/probe; 300 nM HRSV- 1084 (forward primer, 5'GATGGCTCTTAGCAAAGTCAA GTT3'), 300 nM HRSV-1253 (5'CATCTTCWGTGA TTAATARCATRCCACATA3'), 150 nM of HRSV–MGB (probe, VIC-ACAGGAGATARTATTGAYACTC), 2.50 µL of 2X Ag. RT-buffer, 2.0 µL of 25×Ag. enzyme mix, and 4.10µL RNASE-free water. The reaction was carried out in an amplification of 50°C for 30 min, 95°C for 5 min, 45 cycles of 15 s at 95°C and 30 s at 60°C. Subsequently, the RSV positive samples were subtyped to differentiate between RSV-A and RSV-B, using a group-specific real-time multiplex RT-PCR primers to target the RSV G gene as described in a previous study [31]. In this reaction, 5 µL of RSV positive RNA was amplified with 0.6 µL of 600 nM HRSVA-G409 (forward primer, 5'AAGACCAAAAACACAACAACAA3'), 0.3 µL of 300 nM HRSVA-G586Neu (reverse primer, 5'TTGGTA TTCTCTTGCAGATGG3'), 0.2 µL of 150 nM HRSVA-G556 (probe, YAK-5'TTGGATTGTTGCTGCATATGC TGCT3'-BBQ), 0.3 µL of 300 nM HRSVB-G155 (forward primer, 5'CAATGATAATCTCAACCTCTCTCA3'), 0.3 µL of 300 nM HRSVB-G303 (reverse primer, 5'GGTGAG ACTTGAGTAAGGTAAGTG3'),150NmHRSVBG201-(probe,5′6FAMCATCTCTGCCAATCACAAAGTTAC ACTAACAAC3'-BBQ), 2.50 µL of 2X Ag. RT-buffer, 2 µL of 25×Ag. enzyme mix and 3.6 µL RNase-free water. The amplification conditions used were 50°C for 30 min, 95°C for 5 min, 45 cycles of 15 s at 95°C and 30 s at 60°C.

Sequencing of RSV isolates

For sequencing and identification of RSV genotypes, the second hypervariable region (VR2) of the G protein gene was targeted using nested PCR. Extracted RNA of RSV-B samples was initially reverse transcribed, followed by the PCR amplification. The first round of amplification was performed using the primer pair, HRSVB- G524F (5'TTGTTCCCTGTAGTATATGTG3') and HRSVB-F55R (5'AGTTAGGAAGATTGCACTTGA3'). The DNA product from the first reaction was used in a subsequent PCR reaction using the primer pair HRSVB-G603F (5'AAAACCAACCATCAAACCCAC3') and HRSV-F22R (5' CAACTCCATTGTTATTTGCC3') for more specific amplification of the VR2 of the G protein gene. Both PCR amplification conditions were as follows; 94 °C for 5 min, 40 cycles for 30 s at 94 °C, 30 s at 58 °C, 1 min at 72 °C and an extension step at 72 °C for 10 min. The DNA products were analyzed using 2% agarose gel along with 1000 bp molecular weight ladder (BioLabs Inc, New England). Both the PCR products and PCR amplicons excised from the agarose gel were purified using a QIAquick purification kit (QIAGEN, Germany). The purified products were loaded into an ABI 3130XL genetic analyzer (Applied Biosystems, Foster City, CA) and cycle sequenced in the forward direction and reverse direction using BigDye Terminator v3.1.

Sequence and phylogenetic analysis

The sequenced contigs were first assembled using Sequencer v5.4.6. Consensus sequences were then generated, and the sequences were further analyzed using MEGA v11. The RSV-B parental sequence of reference strain 18,537 with accession number M17213 was retrieved from GenBank and aligned with the sequences detected in this study. A represented sequences from Ghana, and other globally circulating ones, as well as closely related sequences obtained from the GenBank

were retrieved and mapped with the sequences from this current study. The multiple alignment sequences created were phylogenetically analyzed employing the neighbor-joining method and bootstrap values based on 1,000 replicates were deemed statistically significant. The evolutionary distances were computed using the Tamura 3-parameter method and are in the units of the number of base substitutions per site. Only bootstraps values above 70% were illustrated on the trees. Using Microsoft Adobe illustrator 2022, the phylogenetic tree was manually edited. The nucleotide sequences identified in this study have been deposited in GenBank (http://www.ncbi.nlm.nih.gov) under the accession numbers PP576222-PP576232. For the amino acid sequence analysis, the BioEdit Sequence Alignment Editor v7.2.5 was employed to translate sequences based on the standard genetic code.

Statistical data analysis

Microsoft Excel was used to record participants' details including age, gender, type of admission, clinical features, medical history, and clinical diagnosis from completed case investigation forms/questionnaire (supplementary sheet 1). This data was then exported to IBM SPSS v23.0 for statistical analysis. Statistical significance was assessed with a P-value of 0.05 or lower. The Chi-square test was used to examine the relationships between clinical symptoms, clinical diagnosis and the occurrence of RSV infection. Real-time PCR results were analyzed in ABI7500 software v2.3.

Results

Demographics and clinical characteristics of enrolled patients

A total of 212 patients who met the ARI case definition were included in this study from March to October 2023;142 (67%) from UGMC, 36 (17%) from KBTH and 34 (16%) from UGHL. Most patients (95.7%) were residents of the Greater Accra Region while only 4.3% came from other regions including the Eastern Region, Central Region, and Western Region to seek medical assistance (Fig. 1). Patients' ages ranged from 50 to 92 years, with a median age of 60. Most of the participants 158 (74.5%) enrolled were outpatients. Among in-patients, 70.4% (38/54) were from the casualty unit, 25.9% (14/54) from emergency units, and 3.7% (2/54) from the ICU. The most common clinical symptom among enrolled patients was cough, occurring in 121 patients (57.1%). Other symptoms included fever (documented as temperature > 37.5 °C) in 4.7% of patients, breathing difficulties in 36.8%, and wheezing in 1.4%. Nineteen patients had underlying chronic health illnesses. For other relevant clinical data, most ARI patients 197 (92.9%) in this study were not aware of RSV disease or had not heard of such a respiratory virus (Table 1). The number of patients who were not aware of the occurrence of RSV disease but

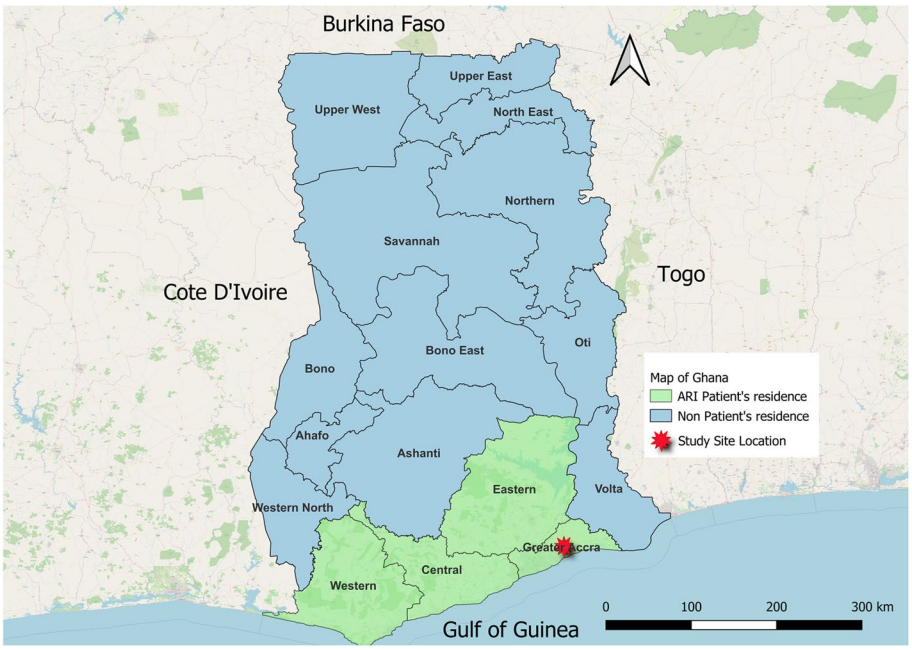

Fig. 1 A map of Ghana showing its 16 Administrative Regions. The three study sites (hospitals); UGMC, KBTH and UGHL are in the Greater Accra Region, marked with a red cardinal point. ARI patients who sought medical assistance from these study sites and were enrolled in this study were residents of Eastern, Central, Western and Greater Accra Region, shown in light green

Table 1 RSV awareness and vaccine acceptance responses from enrolled patients

RSV Awareness	Willingness to receive a vaccine		Total
	No	Yes	
	N (%)	N (%)	N (%)
No	171(80.6)	26(12.3)	197(92.9)
Yes	11(5.2)	4(1.9)	15(7.1)
Total	182(85.8)	30(14.2)	212(100)

were willing to take a vaccine for protection were higher (23%) as compared to those (5.2%) who knew of the virus (Table 1).

RSV detection and disease outcomes

Out of the 212 nasopharyngeal and oropharyngeal samples collected and screened, 11 tested positive for RSV by RT-qPCR analysis, resulting in an incidence rate of 5.2% (Table 2) among the patients enrolled. RSV was detected among all age groups. In Table 2, the higher number of positive patients were adults 65 years and older, however there was no significant difference (p-value = 0.627) as compared to those who were between the ages of 50 and 65. Moreover, the mean age of the RSV patients was 62 years. Concerning the distribution of RSV infections based on gender, females 6 (54.5%) were more infected than males. From the RSV positive cases, more outpatients (7, 63.6%) were infected as compared to the patients on admission.

For clinical diagnosis, 45.5% (5/11) of RSV patients suffered respiratory distress. Pneumonia was recorded in 3 (27.3%) patients while the other 3 were diagnosed with ARI which were not specified (Table 2). Two RSV patients (18.2%) had underlying chronic illnesses; diabetes, CHF. These 2 patients experienced complications with pneumonia and were receiving ventilation support in the ICU (Table 2). Cough was significantly associated with RSV infection (p = 0.023). Other clinical symptoms such as difficulty in breathing were recorded in 6/11 (54.5%) patients while fever was seen in only one person (Table 2).

Predominant RSV group and monthly case distribution

ARI specimens were collected throughout the study period, from March to October 2023 (Fig. 2). RSV differentiation revealed that detected RSV cases were predominantly of the RSV-B subtype, with no cases of RSV-A recorded (Fig. 2). ARI cases and RSV activity correlated with the rainfall periods. Ghana lies in the tropics and often experienced heavy rainfalls between April and October. A peak in RSV-B infections was seen in September and October (Fig. 2). In general, the highest number of ARI cases (101 out of 212, or 47.64%) occurred in August. However, this did not correspond to a higher number of RSV-B infections. Instead, RSV-B cases were more frequently recorded in September and October, when ARI cases had declined.

Table 2 Demographics and clinical characteristics of RSV patients

Characteristics	Total (N)	n	%(n/N), CI	*P*-Value
Total	212	11	5.19(2.61, 9.09)	
Gender				
Male	117	5	4.27 (1.40, 9.69)	0.505
Female	95	6	6.31 (2.35, 13.24)	
Age in years				
50- 64	96	3	3.13 (0.64, 8.86)	0.627
65- 79	83	6	7.23 (2.69, 15.07)	
≥ 80	33	2	6.45 (0.79, 21.42)	
Hospitalization				
Out-patient	158	7	4.43 (1.79, 8.91)	0.394
In-Patient	54	4	7.41 (2.05, 17.89)	
Ventilator Usage				
Yes	26	2	7.69 (0.94, 25.13)	0.808
No	186	9	4.86 (2.24, 9.03)	
Patient diagnosis				
Acute Resp. Infect	121	5	4.13 (1.35, 9.37	0.684
Pneumonia	65	3	5.88 (1.22, 16.24)	
Bronchitis	2	0	0	
ARI unspecified	24	3	7.50 (1.57, 20.38)	
Chronic illnesses				
Asthma	5	0	0	0.447
Hypertension	2	0	0	
CHF	6	1	16.67 (0.43, 64.12)	
Diabetes	6	1	16.67 (0.43, 64.12)	
Symptoms				
Fever (> 37.5)	10	1	4.95 (2.39, 8.91)	0.482
Breathing Difficulty	78	6	7.69 (2.87, 15.99)	0.21
Cough	121	10	8.85 (4.32, 15.67)	0.023
Wheezing	3	0	0	0.683

N Number of study participants, *n* Number of RSV positive patients, *CI* Confidence interval

Sequence and phylogenetic analysis of identified RSV-B sequences

The second VR2 of the glycoprotein G gene of the eleven RSV subtype B isolates were successfully sequenced and assigned genotype numbers. The phylogenetic analysis was based on nucleotide sequences. The tree comprised of the 11 sequences identified in this study, RSV-B parental strain (M17213) and 42 RSV studied strains, including sequences from African countries such as Ghana, Kenya, Gabon, Burkina Faso, Tanzania, Nigeria, Benin, South Africa, and from developed countries

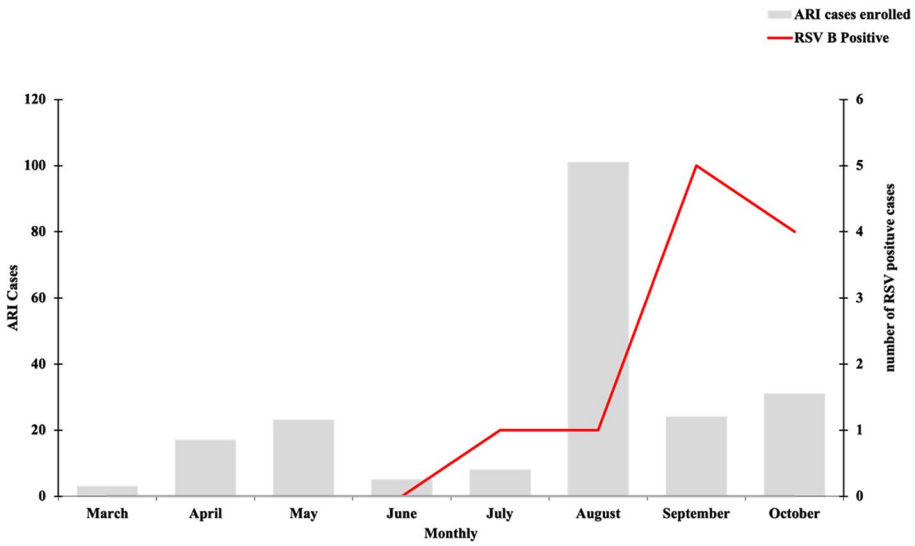

Fig. 2 Monthly distribution pattern of ARI and RSV cases, March-October 2023

like Thailand, Japan, retrieved from NCBI GenBank. The phylogenetic analysis revealed the current study sequences belong to RSVBA9 genotype (Fig. 3). All RSV/BA9 sequences on the tree tend to have formed 4 clusters (cl.1-cl.4). Five of the RSV/BA9 genotypes identified in this study formed a cluster (cl.1) with previously studied sequences from Kenya, supported by a bootstrap value of 74 (Fig. 3). However, the Kenyan genotypes branched differently with a bootstrap value of 95. The remaining 6 RSV/BA9 genotypes form the current study stood out as one cluster (cl.2) but was directly linked to the cl.1 RSV/BA9 genotypes, supported by a bootstrap value of 86. Additionally, the sequences found in this study was closely related to other studied RSV/BA9 genotypes from Burkina Faso, Gabon, Tanzania (cl.3) and that found in Ghanaian infants in 2013 (cl.4). However, the strains from Burkina Faso and Gabon (cl.3) seem to be the closest to the currently identified RSV/BA9 genotypes in cl.2, with a bootstrap of 91 at a major node which branched directly into cl.1 and cl.2 (Fig. 3). Significantly, only RSV/BA9 genotypes were found to be circulating among the adult population in Ghana, from July to October 2023.

Deduced amino acid sequence analysis of RSV/BA9 strains

The second hypervariable G region (VR2 G) of the RSV/BA9 strains identified in this study and closely related studied RSV/BA9 strains from African countries including Burkina Faso, Gabon, Kenya and Ghana were aligned to the prototype strain of RSV-B; M17213 (Fig. 4). Aligned RSV/BA9 strains compare to the RSV-B prototype/parental strain carry 60-nucleotide duplications in the VR2 G region resulting in the insertion of 20 extra amino acid sequences (TERDTSTSQSTVLDTTSKH) from aa 260 to aa 279 (Fig. 4). Like the original BA strains [32]. I28T aa substitution was specific to RSV/BA9 strains identified in this study (Fig. 4). Also, RSV/BA9 cluster 2 (cl.2) strains had an S291P substitution which was unique. Significantly, two strains (RSV092/2023, RSV211/2023) from cl.2 were distinct and showed higher number of aa substitutions as compared to the other identified strains. RSV/BA9 strains from the current study revealed a protein length of 313 aa, although, few of them predict alternative stop codons at aa 320 (Fig. 4). Also, RSV/BA9 (cl.1 and cl.2) from this current study shares identical aa substitutions including I227N, I255T, P257S, Y279H, T315L, H318L with Ghanaian strains identified in infants in 2013. However, P219R and P306L were only specific to the strains found in infants. Also, strain from the current study clustered with previously studied strains from Kenya (cl.1) but comparing their amino acid sequences, RSV/BA9 from Ghana showed additional showed additional substitutions; M222T, I229T, T230I, I245T, S246P, I255T, Y279H, S291N, L309S (Figs. 3 and 4). For other closest genotype matches such as the Burkina Faso and Gabon RSV/BA9 virus, these shared significant similarities in their amino acid sequences. In comparison with current study strains, these viruses showed many different aa substitutions like T214N, T222A, T225D, H280S, Y287 and N296T but shared similar substitutions. e.g. L2370, I246T, S248P, I300T (Fig. 4).

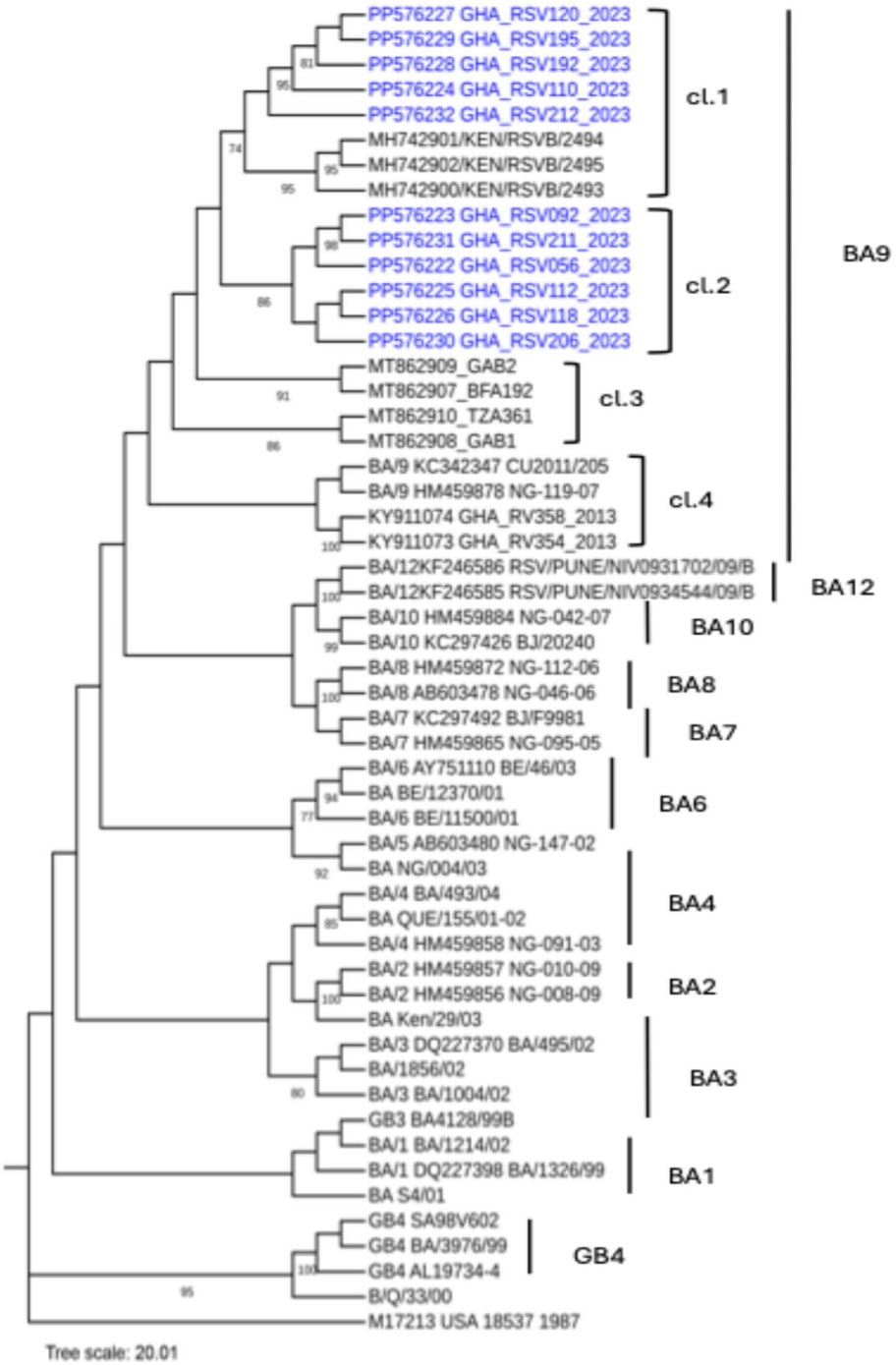

Fig. 3 Phylogenetic analysis of RSV-B strains detected in Ghana adult population, 2023. The evolutionary tree was inferred using the Neighbor-Joining method in MEGA v11. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown below the branches; only bootstrap values of above 70% are shown. The evolutionary distances were computed using the Tamura 3-parameter method. Genealogical lineages, accession numbers, countries, and years of virus collection are indicated from left to right with GenBank reference sequences from several continents. Sequences from the current study are shown in blue

Discussion

The study investigated the molecular epidemiology of RSV among hospitalized and non-hospitalized adults aged 50 years and older at hospitals in Accra (Ghana), from March to October 2023. A sensitive molecular analysis was employed to detect and characterize RSV in the clinical specimens obtained from the older adults who presented with ARI. This is the first study to have

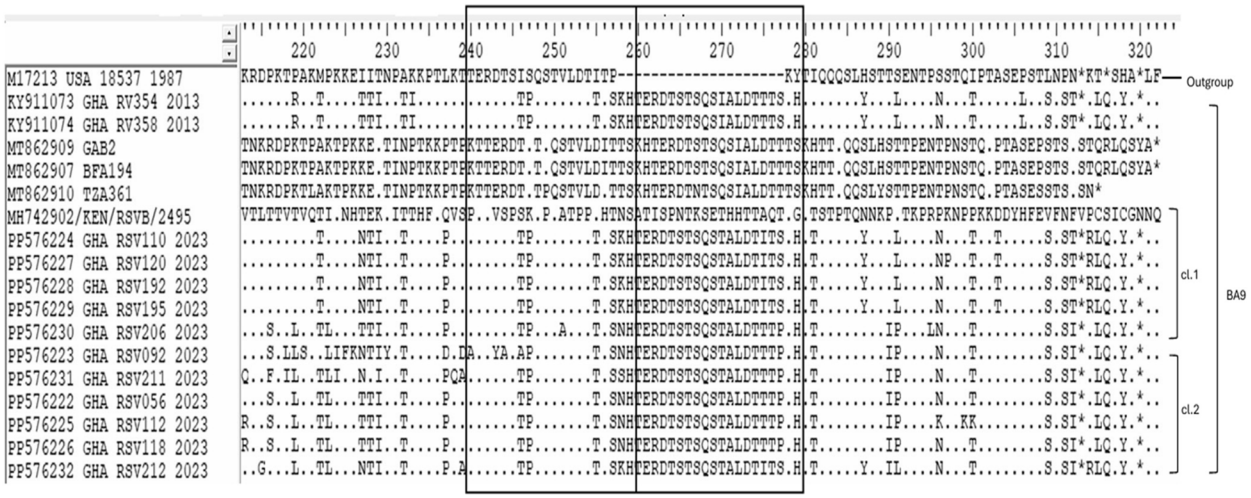

Fig. 4 Alignment of deduced amino acid sequence of the VR2 region of RSV G protein gene of strains identified in this study. Sequence alignments are shown relative to RSV B reference strain 18,537(GenBank accession number, M17213). The amino acid positions correspond to positions 213 to 320 of the G protein of the prototype BA strain. Boxes or rectangles show the amino acid duplicated regions. Identical amino acid residues are indicated in dots (.). Stop codons are shown in asterisks (*)

provided data on the circulation patterns and molecular diversification of RSV among the adult population in Ghana.

The overall incidence rate of RSV was determined as 5.2%. This finding was comparable to the incidence of RSV recorded in 2013 in older adults in Senegal [33]. In contrast, studies from Egypt and Kenya reported lower incidences of 2% and 1.3%, respectively, among adults aged 50 years and older [5, 32]. Some studies have also reported higher RSV-positive rates among individuals aged 50–64, 65–79, and ≥ 80 years as 23.2%, 36.2%, and 27.5% respectively [34]. Generally, discrepancies in detection rates can be related to geographical variations in virus prevalence, the number of patients tested, the timing of sample collection, and the duration of the study [35]. Although, a higher number of clinical samples were collected among adults aged 50 to 64 years, the number of RSV positive cases were 2 times higher in adults aged 65 to 79 than 50- to 64-year-olds, indicating a higher burden of RSV among adults who are at the extreme end of age. This observation was consistent with studies in other developing countries but generally with higher detection rates [34]. Additionally, a similar report from an industrialized country has shown that the estimated number of persons (≥ 65 years) with respiratory diseases attributed to RSV during an RSV season was 2. 3 higher (3917 episodes per 100,000) than persons who were 50–64 years of age (1325 episodes per 100,000) [36]. While RSV infection in children decreases with increase age [24, 37, 38], it appears the adult is more likely to contract the virus as age increases [7, 39, 40]. In this study, less males were infected with RSV as compared to females. However, the difference in the male and female genders as a risk factor for RSV disease is not statistically significant, and this is consistent with other studies in adults and children [24, 37, 41].

The higher number of RSV cases recorded among outpatients as compared to inpatients has been observed as well by other studies [42, 43]. Similarly, among children in LMICs, RSV infections are largely high in the community with increased deaths especially among infants [44]. High community transmission may affect the elderly persons within the population and further result in severity of disease, increase hospitalizations, and even death [8, 45, 46]. Nevertheless, RSV cases from our study were not significantly associated with complications such as pneumonia and bronchitis [42, 47]. Patients most often sought early medical attention and reported ARI as their primary reason for hospital visit. Cough was significantly observed as compared to other clinical symptoms such as running nose, nasal congestion, chest pains, sore throat, shortness of breath and fever [48–50]. CHF and diabetes were the underlying chronic factors that predisposed about 50% of hospitalized RSV patients to severe respiratory illness which required intensive care and ventilation on admission. Similar findings have previously been reported by studies elsewhere [34, 42, 51, 52]. RSV-associated illnesses are known to increase the exacerbation of pre-existing cardiovascular complications [34].

RSV is seasonal [53, 54] and with regards to its circulation, biological specimens were collected throughout an 8-month period which characterizes the RSV season in the

tropics [24, 37, 55]. In our study, RSV cases were recorded from July to October depicting that the incidences of RSV correlated with the wet season which is also typical of other pediatric and geriatric studies from sub-Sahara Africa [33, 49, 56, 57]. However, no RSV cases were detected at the onset of the season. Though it is not clear why it was so, one important observation was that the absence of cases also coincided with delay in rainfall during the period. Recent studies have reported global shifts in RSV seasonality after the COVID-19 pandemic; however, such trends remain to be assessed in Ghana and other tropical regions [58–60]. A robust and continuous molecular surveillance for RSV is needed to prevent the biased sampling periods and contribute to more specific and complete data on RSV seasons and transmission dynamics in Ghana.

RSV differentiation results revealed RSV-B as the only circulating subtype isolated from the clinical specimens that tested positives for the RSV preliminary (RT-qPCR) screening. No cases of RSV-A infection were observed during the study period. However, unpublished data from the RSV GOLD-ICU Network Study, Ghana (2021–2023) indicates both RSV-A and RSV-B subtypes co-circulated in children during this period and even then, the RSV-B infections were 3.5 times higher than that of RSV-A emphasizing the predominance of RSV-B virus in Ghana as compared to other regions where the predominating genotype alternates. Globally, co-circulation of RSV-A and RSV-B has been established to occur with subtype A typically dominating [34, 61, 62]. Nonetheless, single genotype circulation does occur and has also been reported globally [17, 24, 43, 63].

All the studied RSV-B sequences clustered as BA; specifically, genotype BA9. This finding is consistent with recent studies from Ghana [23], Tanzania, Senegal, Burkina Faso [24, 55] and from other continent like Australia [13, 33, 55, 62], indicating the global spread and transmission of the RSV/BA9 variant. RSV/BA9 is a lineage which comes from the ancestral BA genotype which was first identified in Niigata, Japan [17]. Just like the ancestral BA genotype, the identified RSV/BA9 shows a 60-nucleotide duplication in the VR2 region of the G gene which serves as a target for genotype-specific neutralizing antibodies [24]. The phylogenetic and deduced amino acids analysis of identified strains revealed two distinct RSV/BA9 clusters with characteristic amino acid substitutions as compared to their closest matches. Also, most RSV/BA9 strains revealed a protein length of 313 amino acids but few of them were 320 amino acids. These genetic alterations can result in antigen variation, which may offer a survival advantage to viral strains by allowing them to evade the host immune response [64, 65]. Current RSV/BA9 strains clustered with sequences found previously circulating in Kenya [66], Tanzania [55], Burkina Faso [55], Gabon [55], Ghana [24] Thailand [16] and Japan [67]. Studies from the other African countries documented the occurrence of the virus strains in 2004/2005, 2011/2012, 2015 and 2016/2017, suggesting their importation to Ghana before 2023. This has been confirmed by a molecular study in children which reported the circulation of RSV/BA9 in Ghana as early as 2006 and again in 2013 [24]. Additionally, the clustering of some sequences from this current study and that from Kenya, and the time of circulation of both strains suggest possible importations of Kenyan RSV/BA9 strains to Ghana. However, amino acids sequences analysis from the current study revealed the accumulation of substitutions indicating how diverse the viruses have evolved with time. The previously studied RSV/BA9 strains from Ghana, for instance, were responsible severe lower respiratory infections and complications including pneumonia, bronchitis, as compared to the current study where lesser incidence rate and lower mean severity of infections occurred. Strain revolution contributes to viral fitness and disease pathogenesis, highlighting it relevance in the development of RSV vaccine candidates [68]. Therefore, over-reliance on a single strain may exaggerate or underestimate the effectiveness of RSV monoclonal antibodies or vaccines [69].

RSV prevention is attainable as the world have entered an exciting phase in monoclonal antibody and vaccine development [28]. The approval of three vaccines (maternal and vaccine for older adults) and a monoclonal antibody (Nirsevimab for infants) by the Food and Drug Administration (FDA) for use in the developed countries serves as a beacon of hope for RSV intervention strategies in LMICs. Nevertheless, there is poor RSV awareness which can lead to vaccine hesitance. Few, approximately 7% of study participants know of RSV disease and only 14% of participants demonstrated willingness to accept RSV vaccines when they become available. Studies in LMICs have shown that most caregivers lack knowledge about RSV and its associated risks, leading to higher mortality rates in the community [41]. Therefore, increased awareness among the general population and National Health Care providers will be necessary for RSV vaccine implementation and acceptance. More importantly, surveillances on RSV disease burden and molecular evolution in Ghana can contribute to the country's inclusion to participation in vaccine trial studies. This study was limited by a shorter period and sample size, compared to similar previous studies [24, 70].

Conclusion

This study showed the burden of RSV disease is high among adults who are 65 years and older. It also suggests adults in this age category are more susceptible to or are

at a high risk of RSV infection. RSV was more prevalent among non-hospitalized patients as compared to inpatients, suggesting possible infections among community dwelling older adults. In addition to age, this study also identified chronic underlying health conditions such as diabetes and CHF as risk factors for RSV infection or perhaps, a more severe infection which may require intensive care and ventilation on hospital visits. RSV/BA9 remained a persistent variant causing acute respiratory complications in older adults during wet and low temperature season in Ghana. Single distinct strain can circulate, and multiple variants can co-circulate during the same time in other sub-regions of Africa. This molecular study serves as a baseline information for future RSV studies in Ghana and Africa at large. As vaccines for RSV disease in older adults have begun to surface, a greater understanding of RSV seasonality, strain diversity and factors that drive the disease in the older adult populations in LMICs will be necessary to safeguard their inclusion in RSV clinical trials and the availability of therapeutics interventions for treatment and possible prevention.

Abbreviations

ARI	Acute Respiratory Infection
COPD	Chronic Obstructive Pulmonary Disease
CHF	Congestive Heart Failure
EPRC	Ethical and Protocol Review Committee
hMPV	Human Metapneumovirus
KBTH	Korle Bu Teaching Hospital
LMICs	Low- and middle-income countries
LRTI	Lower Respiratory Tract Infection
NMIMR	Noguchi Memorial Institute for Medical Research
PCR	Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-qPCR	Reverse Transcriptase Quantitative Polymerase chain reaction
UGHL	University of Ghana Hospital Legon
UGMC	University of Ghana Medical Center
URTI	Upper Respiratory Tract Infection
U.S CDC	United States Centers for Disease Control and Prevention
VR2	Second Hypervariable Region
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
CNA and EO contributed to conceptualization. BD, CNA and EO designed and implemented the study. CNA, JA, VNLA, ASYA, GGW and JKO participated in acquisition and formal analysis of data. CNA and JAQ provided statistical analysis. CNA and EO contributed to writing-original draft preparation. BD, CNA, EO, JA, VNLA, ASYA, GGW, JAQ and JKO reviewed and revised the draft. All authors have read, approved and agreed to be accountable for the published version of this manuscript.

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Data availability
Sequence data from this study have been deposited in NCBI GenBank (http://www.ncbi.nlm.nih.gov) under the accession numbers PP576222-PP576232. All other data are within the context of this manuscript.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethical and Protocol Review Committee (EPRC), College of Health Sciences, University of Ghana (Reference: CHS-Et/M.6-P5.8/2022–2023). Participation was voluntary and informed consents were obtained from patients before their enrollments in the study. Each participant was informed in plain language of understanding regarding the study aims, methods, anticipated benefits, potential risks, potential conflicts of interest and provisions for privacy protection and confidentiality as declared by HELSINKI. Laboratory codes were used to conceal the identification of study participants. Completed case investigation forms/questionnaire were kept under lock and key at the Department of virology, Noguchi Memorial Institute for Medical Research, University of Ghana.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Virology Department, College of Health Sciences, Noguchi Memorial Institute for Medical Research, University of Ghana, P.O. Box LG 581, Legon, Accra, Ghana. [2]Department of Medical Biochemistry, University of Ghana Medical School, Korle Bu, Accra, Ghana. [3]Medical and Scientific Research Centre, University of Ghana Medical Centre, Legon, Accra, Ghana. [4]Department of Medicine and Therapeutics, Korle Bu Teaching Hospital, Accra, Ghana.

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