

Original Research

Epidemiology and associated factors for hospitalization-related respiratory syncytial virus infection among children less than five years of age in Saudi Arabia. A Real-World Retrospective Analysis

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Received (first version): 07-May-2024

Accepted: 05-Aug-2024

Published online: 23-Jan-2025

Abstract

Background: The rapid development, approval, and distribution of these vaccines highlight the need to carefully assess their safety. One significant concern is the incidence of Adverse Events Following Immunization (AEFI). There are few reports on the factors influencing AEFI and differences in AEFI among different COVID-19 vaccine brands in Thailand. Exploration of the incidence and factors related to post-vaccination adverse reactions against SARS-CoV-2 in the population attending vaccination centers in Thailand is considered pivotal. **Objective:** To investigate the incidence and factors associated with adverse events following the administration of the COVID-19 vaccine in the Ubon Ratchathani province. **Methods:** We analyzed data from individuals who received COVID-19 vaccinations in Ubon Ratchathani province between June 1, 2021, and July 31, 2022. **Results:** The study examined data from 2,955,978 COVID-19 vaccines administered in Ubon Ratchathani province. Among these, 3.34% experienced an AEFI, further categorized into events occurring within 30 min (0.17%) and after 30 min (3.19%) of vaccination. The occurrences were higher in females compared to males. The age groups exhibited distinct AEFI rates, with children aged 5–17 years and adults aged 18–60 years facing a higher risk. Additionally, individuals with comorbidities are more likely to experience AEFI. The brand of the vaccine and the number of doses administered also influenced AEFI rates. This comprehensive analysis provides valuable insights into AEFI reports, vaccine brands, and associated risk factors, and offers crucial information for vaccine safety monitoring and management. **Conclusion:** This COVID-19 vaccine adverse events study revealed that higher odds of adverse events were associated with being female, younger, having comorbidities, brand of vaccines, or getting over two doses. These findings provide valuable real-world safety information regarding different COVID-19 vaccines, aiding healthcare professionals and policymakers in effectively monitoring and managing vaccine-related AEFI.

Keywords: factors; adverse events following immunization (AEFI); covid-19 vaccine; Thailand

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INTRODUCTION

Respiratory Syncytial Virus (RSV) infection is a significant cause of respiratory illness among children worldwide, particularly in those under the age of 5.¹ Respiratory viruses are common worldwide, and environmental, demographic, socioeconomic, and geographic factors influence their frequency and transmission.² Acute respiratory tract infections (ARTIs) are a leading global cause of pediatric morbidity and mortality.³ ARTIs are caused mainly by viruses, with lesser amounts of



bacteria and fungus contributing as well.⁴ Between 40-90% of ARTIs in underdeveloped nations are caused by viral infections.⁵ (RSV) and influenza virus (flu) are expected to cause 58,000 and 76,000 fatalities annually, respectively.⁶ Respiratory infections affect both adults and children, and they are reflected in a large number of hospital and emergency room visits (e.g., in the United States, there are 140,000 to 710,000 flu-related hospitalizations per year), where respiratory viral infection is the most common reason to seek medical care.⁸

In Saudi Arabia, RSV poses a substantial burden on pediatric healthcare services, leading to a considerable number of hospitalizations and associated healthcare costs.⁸ Between 2001 and 2015, RSV infection was responsible for over 23% of acute respiratory diseases in the pediatric population in Saudi Arabia; the majority of these cases involved children under the age of one year.⁹ The polymerase chain reaction test determined that RSV infection caused 53% and 64% of general ward admissions and pediatric intensive care unit (PICU) admissions, respectively, for children aged < 6 years (median five months) hospitalized with bronchiolitis in Saudi Arabia.¹⁰

Despite advancements in medical science and healthcare infrastructure, RSV remains a formidable challenge due to its high transmissibility and propensity to cause severe respiratory illness, including bronchiolitis and pneumonia, especially in vulnerable pediatric populations.¹¹ The burden of RSV-associated hospitalizations extends beyond immediate health impacts, often leading to long-term respiratory complications and economic strain on families and healthcare systems.¹²

Given Saudi Arabia's diverse geographical and climatic conditions, variations in RSV epidemiology and associated risk factors may exist across different regions of the country.¹³ Factors such as crowded living conditions, air pollution, and inadequate access to healthcare services in certain areas may exacerbate the risk of RSV transmission and the severity of illness among children under five years old.¹⁴

This research article aims to provide a comprehensive analysis of the epidemiology of RSV-related hospitalizations among children less than five years of age in Saudi Arabia. By identifying the associated risk factors, including age, gender, preterm birth, underlying medical conditions, and environmental factors, this study seeks to contribute valuable insights into preventing and managing RSV infections in the pediatric population. Understanding the epidemiological trends and risk factors specific to Saudi Arabia can inform targeted public health interventions, vaccination strategies, and clinical management protocols to mitigate the impact of RSV on children's health and well-being in the region.

METHODOLOGY

Study design and population

A retrospective study was conducted at King Fahad Medical City in Riyadh, Kingdom of Saudi Arabia (KSA), based on secondary data analysis of the electronic medical record. The data was collected during the period from January 2019 to December

2023. The inclusion criteria for the study were Age up to 5 years, diagnosis of respiratory infection, and a positive result for a nasopharyngeal swab of RSV in testing using either an RT-PCR assay or fast antigen testing. All patients' clinical data and laboratory test results were gathered. Clinical variables such as patient characteristics, clinical signs and symptoms, medical diagnosis, length of hospital stay, and blood sample laboratory test were also collected. We chose patients whose diagnoses were based on the 10th version of the International Classification of Diseases.¹⁵

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board Institutional Review Board of King Fahad Medical City, Riyadh, KSA under IRB log Number: 23-525.

Data collection

The review of electronic and paper medical charts collected baseline data on each patient, including underlying diseases, length of hospital stay, and diagnosis type (primary diagnosis of RSV infection, co-morbidity with an underlying disease, and complication from another diagnosis). A history of fever, cough, sputum production, dyspnea, rhinorrhea, sneezing, wheezing, sore throat, nausea, cyanosis, pallor, diarrhea, chest discomfort, convulsions, decreased breath sound, and needing mechanical ventilation was among the symptoms and indicators. The pre-term newborn reference was less than 38 weeks gestation.¹⁶ The following conditions were included in collecting underlying diseases: hematological conditions, neurological disorders, gastrointestinal disorders, kidney disorders, and cardiac and pulmonary ailments. Primary or secondary discharge diagnoses could be the underlying medical issues.¹⁷ Furthermore, laboratory analysis blood tests, including those for hemoglobin (Hb), white blood cells (WBC), platelets, neutrophils, eosinophils, monocytes, and lymphocytes, were obtained using an electronics laboratory record on the day of hospital admission or the initial visit.

Data analysis

We first tallied the total number of RSV cases for descriptive data analysis. We separated them into two groups based on the patient admission types: the outpatient department (OPD) and the in-patient department (IPD). We performed univariable and multivariable binomial regression analysis to evaluate RSV-related hospitalizations in young children. The final model, which included variables significant at the 5% significance level, was chosen using the best subset approach. Calculations were made for crude and corrected odd ratios and 95% confidence intervals. P-values less than 0.05 were regarded as statistically significant. In multivariable logistic regression models (adjusted odds ratio: aOR), variables that showed significant relationships with RSV-related hospitalizations and infections in univariable logistic regression models (crude odds ratio: cOR) were retained. For the data analysis, we used SPSS (version 27).



RESULTS

Prevalence of RSV

In five years, 3790 patients were admitted. Subsequently, 593, 633, 755, 817, and 992 patients were admitted from 2019 to 2023. These results can be visualized in Figure 1.

Clinical Characteristics of RSV

The majority of patients were in the age groups of 1-2 years (49.87%) and 0-12 months (33.44%), with fewer patients aged 3-5 years (16.69%). There were slightly more female patients (59.95%) than male patients (40.05%). RSV pneumonia was the most common diagnosis (83.36%), followed by acute bronchitis due to RSV (7.81%) and acute bronchiolitis due to RSV (2.69%). The average length of hospital stay was 15.21 days, with a standard deviation of 22.32 days, indicating considerable variability in the duration of hospitalization. The results are presented in Table 2.

Symptoms associated with RSV

A runny nose was the most common symptom reported, with 15.27% of patients experiencing it. Among hospitalized patients (IPD), the percentage was slightly lower at 14.49%, while in outpatient department (OPD) patients, it was marginally higher at 16.79%. Cough was reported by 10.42% of patients, with a similar distribution between IPD (8.91%) and OPD (13.46%). The sore throat was reported by 4.09% of patients, with a slightly higher prevalence in OPD (5.70%) than in IPD (3.29%). Tables should be placed in the main text near the first time they are cited. These results are tabulated in Table 2.

Laboratory blood test analysis

The mean Hb level was 12.64 ± 3.48 g/dL. The majority (40.32%) had normal Hb levels, while 34.71% had low levels and 24.97% had high levels. Normal range: 11.00 - 16.00 g/dL. The mean WBC count was $11,048.32 \pm 5957.85$ cells/cu.mm. Most patients (73.14%) had average WBC counts, while 0.95% had low counts, and 25.91% had high counts. Typical range: 5000 -

17,000 cells/cu.mm. The mean platelet count was $339,264.52 \pm 162,750.68$ cells/cu.mm. The majority (65.43%) had average platelet counts, while 1.03% had low counts and 33.54% had high counts. Typical range: 140,000 - 450,000 cells/cu.mm. The mean neutrophil percentage was $54.55 \pm 20.04\%$. The results are explained in Table 3.

Factors associated with hospitalized pediatric patients with RSV infection

Children aged two years or younger had a significantly higher odds ratio (OR) of 2.2 (95% CI: 1.93 - 2.5) for the outcome compared to those older than two years. This association remained significant after adjusting for other factors, with an adjusted OR of 5.12 (95% CI: 2.12 - 9.40). Males had a crude OR of 1.9 (95% CI: 1.3 - 1.9) for the outcome compared to females. After adjustment, the association was slightly attenuated but still significant, with an adjusted OR of 1.2 (95% CI: 1.1 - 1.9). Preterm birth was strongly associated with the outcome, with a crude OR 6.4 (95% CI: 3.1 - 6.9). After adjustment, this association remained significant, with an adjusted OR of 2.72 (95% CI: 2.2 - 2.9). The presence of underlying disease showed a crude OR of 3.2 (95% CI: 3.1 - 3.3) for the outcome. However, after adjustment, the association was attenuated but still significant, with an adjusted OR of 1.5 (95% CI: 1.3 - 1.7). The results are explained in Table 4.

DISCUSSION

Based on a review of medical records, this study provided evidence that RSV is a dangerous virus in young children. Hospitalized children with RSV infection were frequently linked to baseline features, underlying illnesses, and presenting symptoms, according to our retrospective investigation. More than half of the hospitalized children were younger than two years old, making up most of the young patients. Previous research from Saudi Arabia and other countries showed more significant proportions of infection in children under one-year-old and also found similar infection rates.^{13,18} The younger

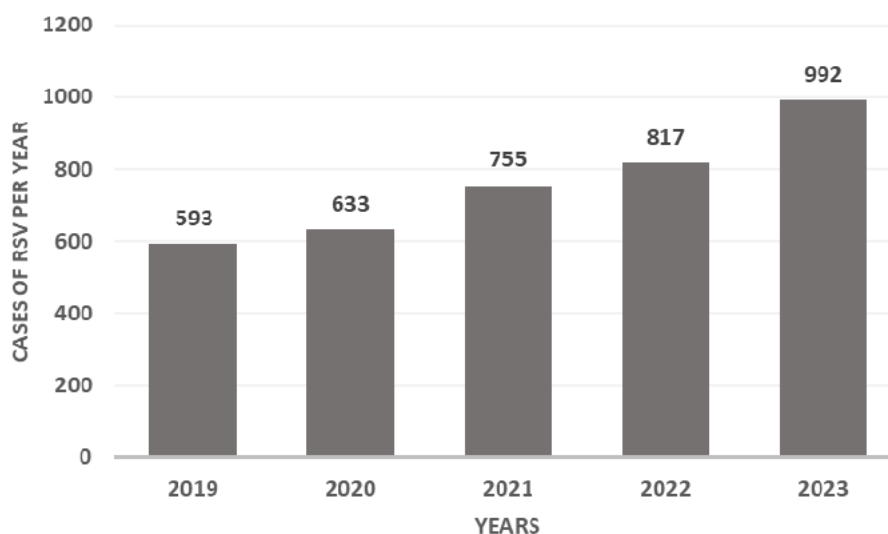


Figure 1. Prevalence of RSV over years 2019-2023



Table 1. Baseline and clinical characteristics of RSV infection in children aged ≤ 5 years (N = 3790)			
Variables	Total	IPD (2527)	OPD (1263)
Age	n (%)	n (%)	n (%)
0–12 months	1267 (33.44)	845 (70.62)	422 (35.14)
1–2 years	1890 (49.87)	1260 (66.67)	630 (33.33)
3–5 years	633 (16.69)	422 (66.67)	211 (33.33)
Gender			
Male	1519 (40.05)	1012 (66.66)	607 (40.13)
Female	2271 (59.95)	1515 (59.96)	909 (59.87)
Diagnosis			
RSV pneumonia	3159 (83.36)	2106 (83.37)	1053 (83.38)
Acute bronchitis due to RSV	296 (7.81)	98 (3.88)	198 (15.67)
Acute bronchiolitis due to RSV	102 (2.69)	34 (1.34)	68 (5.38)
RSV is the cause of diseases classified elsewhere	233 (6.15)	78 (3.08)	155 (12.27)
Diagnosis Type Distribution:			
Primary	3160 (83.38)	2107 (83.44)	1053 (83.38)
Co-morbidity	364 (9.60)	121 (4.79)	243 (19.25)
Preterm birth	266 (7.01)	89 (3.52)	177 (14.03)
Underlying Disease Distribution			
Hematology condition	947 (25.01)	631 (24.98%)	316 (25.00%)
Cardiac disease	758 (20.00)	505 (19.99%)	253 (20.02%)
Pulmonary condition	568 (14.98)	379 (15.00%)	189 (14.96%)
Neurological disorder	379 (10.00)	253 (9.99%)	126 (9.97%)
Kidney disorder	190 (5.01)	127 (5.02%)	63 (4.98%)
Gastrointestinal condition	190 (5.01)	127 (5.02%)	63 (4.98%)
Length of Hospital stay	15.21 ± 22.32	5.21 ± 22.32	

Table 2. Presenting symptoms of RSV infection in children aged ≤ 5 years (N = 3790)

Presenting symptoms	Total	IPD	OPD
	n (%)	n (%)	n (%)
Rhinorrhea	578 (15.27%)	366 (14.49%)	212 (16.79%)
Cough	395 (10.42%)	225 (8.91%)	170 (13.46%)
Sore throat	155 (4.09%)	83 (3.29%)	72 (5.70%)
Sputum production	112 (2.96%)	69 (2.73%)	43 (3.40%)
History of fever	322 (8.49%)	236 (9.34%)	86 (6.81%)
Sneezing	229 (6.04%)	154 (6.10%)	75 (5.94%)
Decreased breath sounds	163 (4.30%)	98 (3.88%)	65 (5.14%)
Dyspnea	361 (9.52%)	258 (10.21%)	103 (8.15%)
Wheezing	220 (5.81%)	140 (5.54%)	80 (6.33%)
Nausea/vomiting	300 (7.92%)	192 (7.60%)	108 (8.54%)
Hemoptysis	158 (4.17%)	97 (3.84%)	61 (4.83%)
Pallor	125 (3.30%)	89 (3.52%)	36 (2.85%)
Cyanosis	98 (2.59%)	61 (2.41%)	37 (2.93%)
Chest pain	221 (5.83%)	132 (5.22%)	89 (7.04%)
Diarrhea	353 (9.32%)	209 (8.27%)	144 (11.39%)

Table 3. Laboratory blood test results of patients with RSV infection			
Laboratory tests	Mean $\pm$ SD	n (%)	Normal ranges
Hb (g/dL)	12.64 $\pm$ 3.48		11.00 - 16.00 g/dL
Normal		1019 (40.32)	
Low		877 (34.71)	
High		631 (24.97)	
WBC (cell/cu.mm.)	11,048.32 $\pm$ 5957.85		5000 - 17,000 cells/cu.mm.
Normal		1849 (73.14)	
Low		24 (0.95)	
High		654 (25.91)	
Platelets	339,264.52 $\pm$ 162,750.68		140,000 - 450,000 cells/cu.mm.
Normal		1654 (65.43)	
Low		26 (1.03)	
High		847 (33.54)	
Neutrophils	54.55 $\pm$ 20.04		40 - 74%
Normal		1072 (42.42)	
Low		522 (20.66)	
High		933 (36.91)	
Eosinophils	1.21 $\pm$ 2.11		0 - 7%
Normal		2144 (84.77)	
Low		43 (1.70)	
High		340 (13.4)	
Monocytes	7.79 $\pm$ 4.99		3 - 9%
Normal		1582 (62.61)	
Low		268 (10.61)	
High		677 (26.78)	
Lymphocytes	36.40 $\pm$ 17.65		19 - 48%
Normal		1264 (50)	
Low		464 (18.36)	
High		799 (31.64)	

Table 4. Binary logistic regression analysis identifying factors associated with hospitalized patients with RSV infection						
Characteristics	Crude OR	95% CI (Lower)	95% CI (Upper)	Adjusted OR	95% CI (Lower)	95% CI (Upper)
(reference group: > 2 years)						
Age $\leq$ 2 years	2.2	1.93	2.5	5.12	2.12	9.40
(reference group: female)						
Male	1.9	1.3	1.9	1.2	1.1	1.9
Preterm birth	6.4	3.1	6.9	2.72	2.2	2.9
(reference group: no underlying disease)						
Underlying disease	3.2	3.1	3.3	1.5	1.3	1.7
(reference group: no symptom)						
Presenting symptoms						
Rhinorrhea	1.2	1.1	1.6	1.9	1.1	1.9
Cough	0.21	0.12	0.20	0.67	0.4	2.5
Sore throat	0.5	0.1	1.2	0.42	0.2	3.6

Sputum production	2.2	1.3	2.5	0.04	0.01	0.06
History of fever	2.1	2.1	2.9	1.3	1.2	1.5
Sneezing	1.2	0.7	3.1	1.9	0.4	3.1
Decreased breath sounds	1.9	1.2	1.9	2.2	0.98	4.2
Dyspnea	1.8	1.1	1.8	1.6	0.1	3.2
Wheezing	2.2	1.4	3.6	2.1	0.8	5.6
Nausea/vomiting	1.9	1.1	1.9	1.5	1.1	1.8
Laboratory blood tests (reference group: normal)						
Low level of Hb	3.5	2.1	3.9	0.24	0.8	1.9
Low level of WBCs	1.4	1.1	4.3	0.5	0.9	1.06
Low level of platelets	01.8	1.5	3.9	0.2	0.7	2.3

age groups are more susceptible to infections, possibly as a result of increased pathogen exposure, weakened maternal antibodies that prevent viral infections after six months of life, low viral clearance from immature immunity, and unsanitary living conditions.^{9,19}

In this study, pulmonary and cardiovascular diseases were prevalently present, with young children or newborns making up the majority of the patient population. The majority of hospitalized RSV patients experienced several symptoms. Usually, these symptoms don't appear all at once; they come on gradually. RSV-associated LRTI is still very common in infants, especially in those under the age of one year.²⁰ Co-morbidities of prematurity, low birth weight, cardiac disease, gastrointestinal problems, and neurological disorders were other correlation findings for risk variables in the prior study.²¹

In young children, gender was a factor linked to RSV infection (Table 4). According to our research, the male gender was protective against hospital-related RSV infection in children, with an odds ratio of 1.2 (95% confidence interval [CI] = 1.1–1.9). In contrast to earlier research, this study produced different findings.^{22,23} From the evidence base, a boy infected with RSV in infancy was associated with developing asthma in adolescence.²⁴ It's plausible that despite having identical exposure to respiratory pathogens, boys were more likely to acquire infections severe enough to require hospitalization because they had a higher frequency of underlying asthma. However, there could be other reasons at play.²⁵ Therefore, keeping a close eye on male patients' RSV infection is important.

Pneumonia was communal in our study and was similar to the previous studies.²⁹ In hospitalized patients, pneumonia caused by RSV was present in 83.36% of children (Table 1). The clinical signs and symptoms of pneumonia are fever, difficulty breathing, dyspnea, and wheezing in general. In our study, we might assume the frequency of the presenting symptoms related to pneumonia with RSV. Similar findings were made by Turner and colleagues (2012), who discovered that patients who presented at a younger age had a significantly higher likelihood of having RSV detected (OR = 21.2, 95% CI = 5.1–88.2, $p < 0.001$).³⁰ They also discovered that RSV-associated pneumonia was more severe in the youngest age group (less than five years).

Infants experienced reduced lung development, insufficient immunity, or a higher risk of catching a respiratory disease from a household member.³¹ This study's results showed that low Hb levels were associated with RSV-related hospitalization in children (cOR = 3.5, 95 % CI = 2.1–3.9. Our results support that RSV infection is associated with decreased Hb in children. Our findings support the theory that childhood RSV infection is linked to reduced Hb. Therefore, we believe this virus—at least the ones frequently found in our hospital—has something to do with how RSV affects hemoglobin. A comparison investigation between Taiwanese infants (less than five years old) infected with RSV and those without bacterial co-infection was carried out in 2022 by Lin et al.³² Reduced hemoglobin levels (aOR = 1.36; 95% CI = 1.01–1.89, $p = 0.042$) were associated with an increased risk of hospitalization for red-blood cell illness.³³ RSV's specific mechanism of action on Hb is unknown.³⁴

It is abundantly evident from the data that several variables are linked to RSV infection and negatively impact newborns. Although they are constantly being researched, vaccines are the most effective means of preventing respiratory diseases. On the other hand, a single dosage of monoclonal antibodies (mAbs) in high-risk populations may be sufficient to prevent RSV infections throughout the RSV season.³⁵ Children in Saudi Arabia who are susceptible to RSV infection have not been given mAbs. Treatments have only been given to RSV-infected children depending on their clinical presentations. Therefore, taking precautions based on transmission is the most effective strategy to stop the spread of infection through contact and drop-let pathways. To enhance treatment outcomes, specific treatments for RSV-associated LRTI need to be investigated, and children who have a history of low Hb levels should exercise particular caution. To lessen the burden of the illness, the public health system should also suggest looking into laboratory blood tests for kids with respiratory infections.

There were various restrictions on this investigation. First of all, it happened in a single site and might not apply to other regions. Furthermore, since this was a retrospective study, some data might have been missing. Third, the study's data were taken from ICD-10 codes, which are prone to error.



CONCLUSIONS

RSV is a major reason for young children's hospital admissions. Our results showed that the primary factors linked to RSV-related hospitalizations were underlying illness and presenting symptoms, particularly sputum production preterm birth in young children under the age of five years. Furthermore, a major contributing factor to children being hospitalized with RSV infection was their low hemoglobin level and pneumonia. The significance of increasing public awareness of the cause of RSV infection in this community has to be highlighted in light of these facts.

AUTHOR CONTRIBUTIONS:

Conceptualization: HMA. GMA MKA and AAA; methodology: NAA, ASA, RHA; software: AAA, SPA, SAD; validation: NMA, ENA, FSA, AMA; formal analysis: HOA MAK; investigation: GMA, AAA, MAA, ASA; resources: MAK; data curation: RHA,

SPA, ENA, NMA; writing-original draft preparation: HMO, FSA, AMA, RHA, MAK; writing-review and editing: HMO. SAD, NMA, ENA; visualization: MAK, HOM; supervision: HOM, MAK; project administration: MAK, HOM; funding acquisition: MAK. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENT:

The authors would like to thank the Research Center at King Fahd Medical City, Riyadh Second Health Cluster, for their valuable technical support provided for the manuscript.

CONFLICTS OF INTEREST:

The authors declare no conflicts of interest.

FUNDING:

This research received no external funding.

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