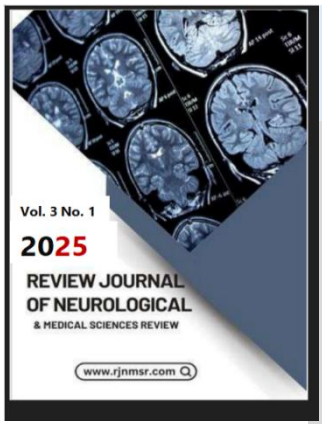

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Molecular and Clinical Evaluation of Human Adenovirus in Children with Upper Respiratory Tract Infections in Peshawar

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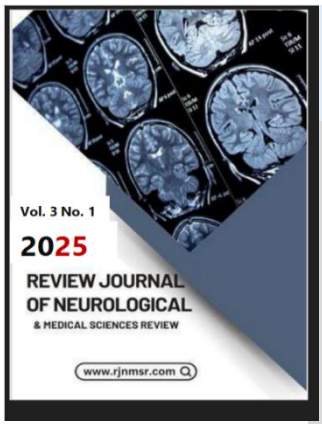

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Abstract

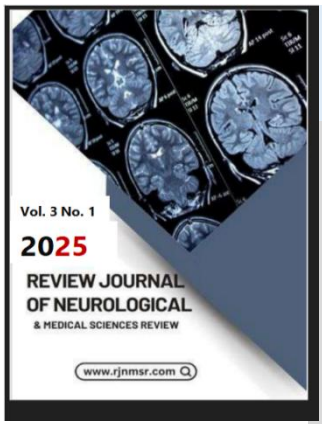
Upper respiratory tract infections (URTIs) are among the most common illnesses in children and often lead to inappropriate antibiotic use. Human Adenovirus (HAdV) is a significant but underreported viral cause of URTIs, particularly in developing countries such as Pakistan. To determine the prevalence of Human Adenovirus (HAdV) among children with URTI using molecular methods and to analyze associated demographic, clinical, and feeding factors, along with patterns of antibiotic usage. A cross-sectional study was conducted among 93 children presenting with URTI at tertiary care hospitals in Peshawar. Demographic and clinical data were collected using standardized questionnaires. Polymerase Chain Reaction (PCR) testing was used to detect HAdV from throat swabs. Data were analyzed for age, gender, feeding behavior, symptom profile, and antibiotic usage. Out of 93 children, 52 (55.9%) were male and the majority (55.9%) were preschool-aged. Bread-only feeding was the most common dietary practice (39.8%). Common symptoms included runny nose (91.4%), fever (83.9%), and cough (81.7%). Antibiotics were prescribed in 95.7% of URTI cases. PCR detected HAdV in 32.3% (30/93) of children. HAdV positivity was highest among toddlers (50%) and in children consuming bread-based diets (46.7%). Runny nose (100%), cough (80%), and fever (76.7%) were the most frequent symptoms among HAdV-positive patients. All HAdV-positive children received antibiotics despite the viral etiology. HAdV is a significant viral pathogen in pediatric URTI cases in Peshawar, particularly affecting children under five. Over-prescription of antibiotics was observed even in confirmed viral cases, highlighting a critical public health concern. Improved diagnostic surveillance, awareness on rational antibiotic use, and investment in HAdV vaccine development are urgently needed.

Keywords: Human Adenovirus, URTI, PCR, Pediatric Infections, Antibiotic Misuse, Feeding Practices

Introduction

Upper respiratory tract infections (URTIs) represent one of the most prevalent global health concerns, particularly affecting pediatric populations. These infections involve the upper segments of the respiratory tract, including the nasal cavities, paranasal sinuses, pharynx, larynx, trachea, and bronchi (Kho et al., 2013; Spurling et al., 2013). URTIs encompass a range of conditions such as the common cold, rhinitis, tonsillitis, pharyngitis, nasopharyngitis, sinusitis, and bronchitis (Cooper et al., 2001). Clinically, they are often characterized by symptoms including sore throat, cough, nasal congestion, fever, sneezing, vomiting, anorexia, irritability, coryza, hoarseness, and conjunctival irritation. Despite being largely self-limiting, URTIs may lead to significant morbidity and healthcare burden, especially in children (Meydani et al., 2004).

Although URTIs in children are typically less severe, they contribute to high rates of pathogen transmission and global outbreaks (Nevin et al., 2011). The predominant etiological agents are viral, with over 200 viral strains implicated. These include



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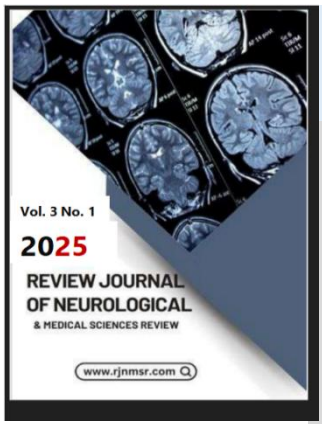
rhinoviruses, parainfluenza, influenza, adenovirus, coronavirus, respiratory syncytial virus, human metapneumovirus, enterovirus (notably mid-year), and bocavirus (Simoes et al., 2006; Allander, 2008). Among these, human adenoviruses (HAdVs) are major contributors to respiratory illnesses year-round. Different HAdV species and serotypes are associated with a spectrum of respiratory diseases occurring in endemic, epidemic, sporadic, and institutional settings (Moura et al., 2007).

HAdVs are linked not only to upper respiratory conditions such as pharyngitis, tonsillitis, and pharyngoconjunctival fever but also to more severe illnesses like pneumonia, otitis media, conjunctivitis, gastroenteritis, hemorrhagic cystitis, and, rarely, central nervous system infections including encephalitis and meningitis (Filho et al., 2007). These infections are especially severe in infants, immunocompromised individuals, and transplant recipients. Several host factors influence infection severity in children, such as age, immune maturity, exposure to other infected individuals, and airway anatomy (Adkins et al., 2004). Unlike adults, children lack prior immunological memory against common respiratory viruses, leading to heightened vulnerability. With age and repeated exposures, adaptive immunity reduces the risk of reinfection (Pihlgren et al., 2003).

HAdV infections are highly contagious and transmitted via respiratory droplets, direct contact, and contaminated surfaces. They possess an incubation period of 2–14 days and remain contagious during the initial phase of illness (Garnett et al., 2002). Unlike other respiratory viruses, HAdVs lack distinct seasonal patterns and are detected throughout the year. In Asia, HAdV prevalence among acute respiratory tract infection (ARTI) cases ranges from 8% to 30% (Guo et al., 2012; Yu et al., 2012). Regional studies report HAdV prevalence rates of 4.5–25% in pediatric populations—10.4%–20.1% in China (Liu et al., 2014), 17.9% in Italy (Fabbiani et al., 2009), and 25% in Brazil (Bezerra et al., 2011).

URTIs are highly endemic and easily spread among children, with pharyngitis, rhinitis, and laryngitis being the most frequent forms. Children may experience 4–7 episodes annually, with toddlers exhibiting the highest incidence (Bloom et al., 2007). Globally, respiratory infections contribute to more than 50 million deaths per year, disproportionately affecting low-resource countries. In developed nations, viral URTIs remain a leading cause of pediatric hospital admissions, whereas in developing countries, they are a major cause of child mortality (Weber et al., 1998). The Centers for Disease Control and Prevention (CDC) estimates that in the United States, children under two years experience 11–33 million URTI episodes annually, resulting in over 2.6 billion missed school days and 23 million lost workdays for caregivers (Bloom et al., 2007). Reported URTI prevalence is 52% in India, 58.7% in Bangladesh (Prajapati et al., 2011), and 16% in Pakistan, where data specific to HAdV-induced URTI remain unavailable (National Nutrition Survey of Pakistan, 2016).



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Multiple environmental and socioeconomic factors exacerbate the burden of pediatric URTIs. These include malnutrition, overcrowding, indoor air pollution, poor ventilation, tobacco exposure, industrial emissions, low socioeconomic status, and inadequate healthcare access (Monto, 2002). Co-morbid conditions such as HIV, prematurity, measles, and lack of parental awareness further contribute to high morbidity and mortality. Of particular concern is the widespread misuse of antibiotics for viral URTIs. Antibiotics, although effective against bacterial pathogens, offer no therapeutic benefit against viruses (Jetacar, 1999). Their unnecessary use can lead to antimicrobial resistance, adverse effects, prolonged illness, and increased healthcare costs (Gilany, 2000). Common contributors to antibiotic misuse include self-medication, cultural practices, physician overprescription, and lack of public health education (Sarahroodi et al., 2010; Bush, 2007).

Despite the global significance of HAdV in pediatric URTIs, there is a scarcity of local data from Pakistan. Therefore, this study was designed to detect and evaluate the presence of human adenovirus in children with upper respiratory tract infections using polymerase chain reaction (PCR), addressing a critical gap in the current epidemiological understanding of respiratory viruses in the region.

Materials and Methods

Study Area

This study was conducted to assess the prevalence of Human Adenovirus (HAdV) in children presenting with upper respiratory tract infections (URTIs) at three major tertiary care hospitals in District Peshawar, Pakistan. These hospitals included Hayatabad Medical Complex (HMC), Khyber Teaching Hospital (KTH), and Lady Reading Hospital (LRH). Nasal samples were collected from the outpatient departments (OPDs) of these healthcare facilities over a period spanning from January to August 2018.

Study Population

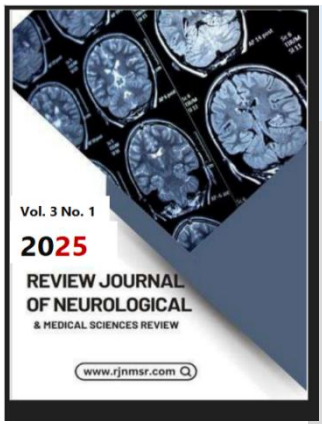
The study population comprised children under the age of 10 years, regardless of gender or socioeconomic background, who visited the OPDs of the aforementioned hospitals with flu-like symptoms. These children represented a wide demographic range and were evaluated based on standardized clinical and demographic criteria.

Inclusion Criteria

Participants were included if they were less than 10 years of age and exhibited clinical signs and symptoms indicative of URTI. Children with a confirmed diagnosis of other respiratory conditions not classified under URTIs were excluded to maintain specificity of data.

Data Collection and Demographic Assessment

A total of 93 children who fulfilled the inclusion criteria were enrolled in the study. Among them, 52 were male and 41 were female. Informed consent was obtained from the parents or legal guardians of each participant prior to data collection. A structured



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and pre-tested questionnaire (Annexure-I) was administered to gather comprehensive demographic and clinical information. Variables recorded included age, gender, type of feeding, presence and nature of clinical symptoms, history of past infections, antibiotic usage, and household health-related factors.

Age was categorized into four developmental stages according to World Health Organization (WHO) guidelines (WHO, 2013): infants (less than 1 year), toddlers (1 to 3 years), preschool children (3 to 5 years), and school-age children (5 to 10 years). Feeding behavior was classified based on the child's primary source of nutrition, including breast milk, formula milk, cow's milk, bread, and combinations such as bread with cow's milk. This categorization helped examine nutritional factors that might influence susceptibility to respiratory infections.

Clinical variables assessed included presence of nasal discharge (runny nose), production of sputum (throat swab), sneezing, wheezing during sleep, nasal obstruction, sore throat, coughing, ear infections, and diarrhea. Additional metrics were also considered: frequency of URTI episodes per year, duration of previous infection episodes, and frequency of antibiotic use during illness. These indicators helped evaluate the severity, recurrence, and clinical management of URTIs among the pediatric population.

Sample Collection

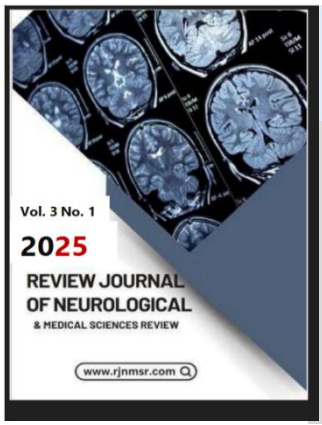
Nasal specimens were collected using sterile swab sticks under standardized procedural protocols. Each swab stick was gently inserted into the patient's nasal passage and massaged to absorb secretions. In cases where visible nasal secretions were absent, the swab was rotated against the inner mucosal surface to collect epithelial cells. It was ensured that the swab bud was adequately moistened or visibly contained mucosal material. Each sample was properly labeled and immediately transported in cold chain conditions to the Molecular Biology and Virology Laboratory, Department of Zoology, University of Peshawar, for molecular analysis.

Laboratory Analysis

DNA Extraction

Viral DNA was extracted from the nasal swab samples using the Trizol reagent protocol. Initially, swab sticks were immersed in 1 ml of normal saline for five minutes and then rubbed against the interior of Eppendorf tubes to release the viral content. To extract nucleic acids, 500 µl of Trizol reagent was added to 100 µl of each sample, and the mixture was incubated at room temperature for five minutes. Following this, 100 µl of chloroform was added and the mixture was again incubated for 2–3 minutes. The tubes were centrifuged at 12,000 × g for 15 minutes, resulting in three distinct layers: an upper aqueous phase, an interphase, and a lower red phenol-chloroform phase.

The aqueous phase, which contains the RNA and DNA, was discarded. The remaining solution was treated with 150 µl of 100% ethanol and incubated for 2–3 minutes to facilitate precipitation. This was followed by a second centrifugation at 2,000



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× g for five minutes, after which the supernatant was removed. To purify the DNA further, 500 µl of sodium citrate (0.1 M in 10% ethanol, pH 8.5) was added and the mixture was incubated for 30 minutes with gentle inversion. The sample was then centrifuged again at 2,000 × g for five minutes, and the supernatant was discarded.

A wash step was performed using 750 µl of 75% ethanol, and the DNA pellet was air-dried for 10 minutes. Finally, the pellet was rehydrated in 150 µl of 8 mM NaOH for downstream molecular applications.

DNA Amplification

For the detection of Human Adenovirus, specific primers targeting the viral genome were used in the polymerase chain reaction (PCR) assay. The forward primer sequence was 5'-GCC ACG GTG GGG TTT CTA AAC TT-3', and the reverse primer was 5'-GCC CCA GTG GTC TTA CAT GCA CAT C-3'. The PCR mixture contained 1 µl of Taq buffer, 2.4 mM $MgCl_2$, 1 µl of each primer, 1 µl of dNTPs, 6.6 µl of deionized water, and 1 µl of Taq DNA polymerase. For each reaction, 20 µl of total volume was prepared, which included 5 µl of the extracted DNA.

PCR was performed using a thermal cycler (Cell Bioscience, USA). The thermocycling conditions were as follows: initial denaturation at 95°C for 5 minutes, followed by 25 cycles of denaturation at 95°C for 30 seconds, annealing at 68.3°C for 30 seconds, and extension at 72°C for 40 seconds. A final extension was carried out at 72°C for 5 minutes.

Gel Electrophoresis

PCR products were resolved using 1.5% agarose gel electrophoresis prepared in 10× TBE buffer. Ethidium bromide (15 µl) was added to the gel for visualization. Prior to loading, 2 µl of loading dye was added to each PCR product. Twelve microliters of the amplified DNA were then loaded into each well. Electrophoresis was conducted for 60 minutes at 120 volts and 500 mA. The DNA bands were visualized using a UV transilluminator to confirm the presence or absence of HAdV DNA.

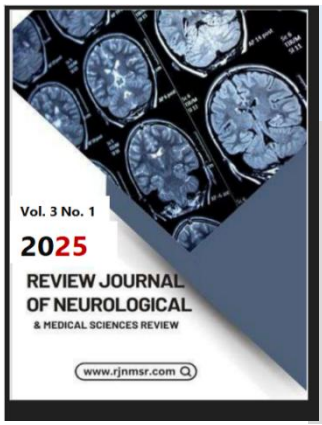
Statistical Analysis

Statistical analysis was conducted using the **Chi-square (χ^2) test** to evaluate the association between HAdV infection and the various demographic and clinical variables. A p-value of less than 0.05 ($P < 0.05$) was considered statistically significant for determining correlations or differences within groups.

Results

General Characteristics of the Study Population

A total of 93 children diagnosed with Upper Respiratory Tract Infections (URTI) were enrolled in the study. Among them, 52 (55.9%) were male and 41 (44.1%) were female. The age distribution followed the WHO classification: infants (<1 year) constituted 20 (21.5%), toddlers (1–3 years) 18 (19.4%), preschool children (3–5 years) 52 (55.9%), and school-going children (<10 years) 3 (3.2%). Feeding practices among participants included: exclusive breastfeeding (14, 15.1%), formula feeding (9, 9.7%), cow milk (16,



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17.2%), bread (37, 39.8%), and a combination of bread and cow milk (17, 18.3%) (Table-1)

Table-1: Demographic Characteristics of the Study Population (n = 93)

Variables	Category	Frequency n (%)
Gender	Male	52 (55.9%)
	Female	41 (44.1%)
Age Group (years)	<1 (Infants)	20 (21.5%)
	1–3 (Toddlers)	18 (19.4%)
	3–5 (Preschool)	52 (55.9%)
	5–10 (School-going)	3 (3.2%)
Feeding Behavior	Mother Milk	14 (15.1%)
	Formula Milk	9 (9.7%)
	Cow Milk	16 (17.2%)
	Bread	37 (39.8%)
	Bread + Cow Milk	17 (18.3%)

Clinical Signs and Symptoms of URTI

The table illustrates the prevalence of various clinical symptoms in 93 children diagnosed with upper respiratory tract infections (URTI). The most common symptoms were runny nose (91.4%), fever (83.9%), and cough (81.7%), indicating these are key clinical indicators of URTI in pediatric patients. Other frequently observed symptoms included sneezing (55.9%), wheeze (51.6%), and nasal obstruction (49.5%), suggesting significant upper airway involvement. Less common symptoms were sore throat (28.0%), sputum production (22.6%), ear infection (17.2%), and diarrhea (9.7%). Throat swab positivity was recorded in 16.1% of the children. These findings highlight that while respiratory symptoms predominate, systemic and gastrointestinal signs may also be present in a subset of children with URTI (Figure-1)

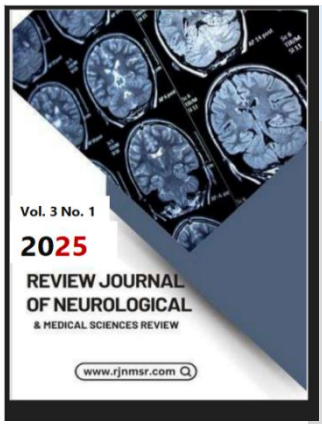

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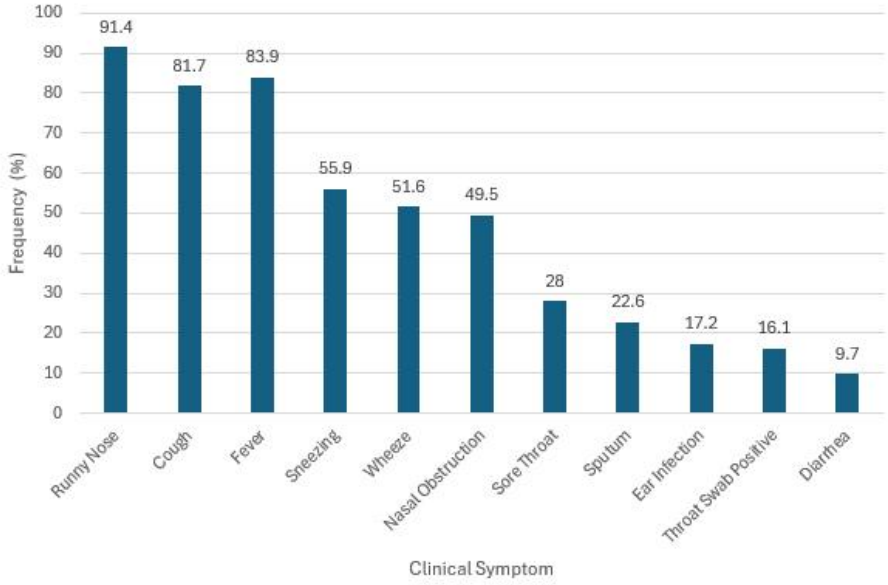
Figure-1: Frequency of URTI Symptoms in the Study Population (n = 93)



Use of Antibiotics Among Children with URTI (n = 93)

A very high proportion (95.7%) of children diagnosed with upper respiratory tract infection (URTI) were treated with antibiotics. This suggests a potential overuse of antibiotics, which is important to monitor, as most URTIs in children are viral and may not require antibiotic therapy (Figure-2)

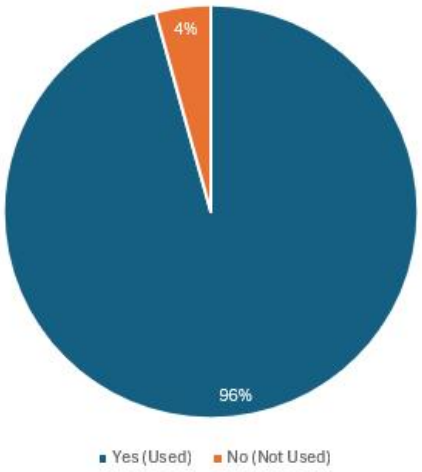
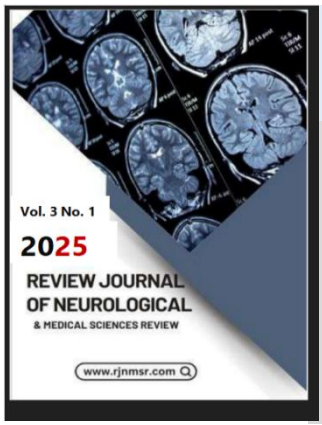


Figure-2: Use of Antibiotics Among Children with URTI (Percentage)



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Overall Prevalence of Human Adenovirus (HAdV) by PCR among Children with URTI (n = 93)

Out of 93 children with URTI, 32.3% were found to be HAdV positive using PCR testing. The remaining 67.7% tested negative for HAdV, indicating other potential viral or bacterial etiologies for their symptoms. This shows that HAdV is a common viral pathogen among children presenting with URTI **(Figure-3)**.

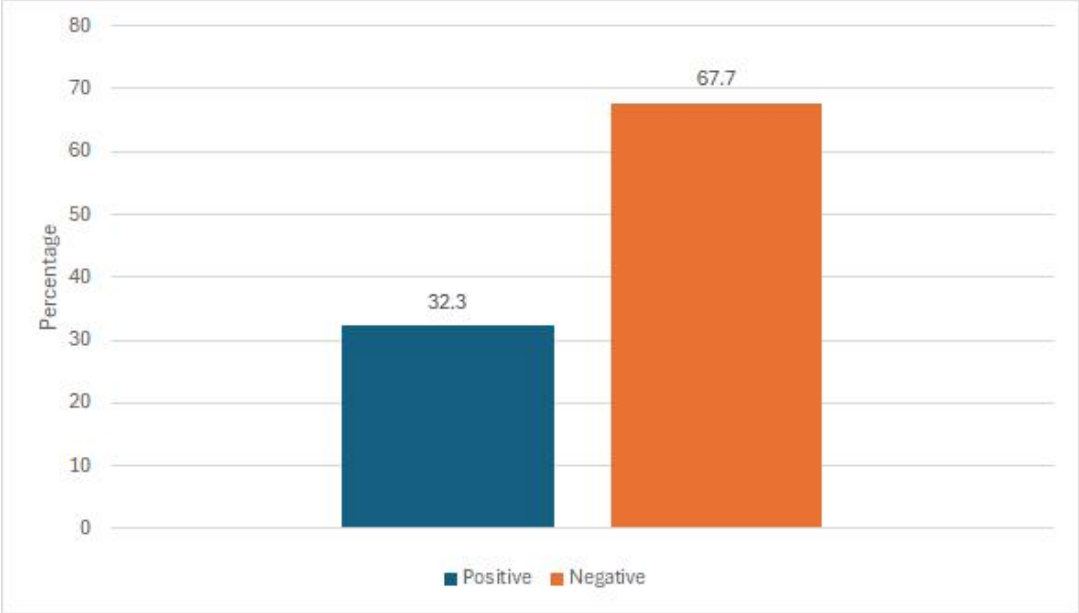


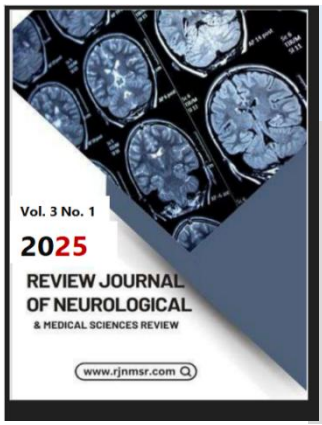
Figure-3: Overall Prevalence of Human Adenovirus (HAdV) by PCR

HAdV Prevalence by Gender

The table presents the gender-wise distribution of Human Adenovirus (HAdV) positivity among 93 children with upper respiratory tract infections. Out of 52 male children, 18 (34.6%) tested positive for HAdV, while 34 (65.4%) were negative. Among the 41 female children, 12 (29.3%) were positive and 29 (70.7%) were negative. Although HAdV prevalence was slightly higher in males compared to females, the difference was not substantial, indicating that HAdV infection affects both genders relatively equally in this pediatric population (Table-2).

Table-2: HAdV Prevalence by Gender (n = 93)

Gender	Positive n (%)	Negative n (%)
Male	18 (34.6%)	34 (65.4%)
Female	12 (29.3%)	29 (70.7%)



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HAdV Prevalence by Age Group

The table summarizes the age-wise prevalence of Human Adenovirus (HAdV) among children with upper respiratory tract infections. Out of the 30 HAdV-positive cases, the highest prevalence was observed in children aged 1–3 years, accounting for 15 cases (50.0%). This was followed by the 3–5 years age group with 9 cases (30.0%). Infants under 1 year made up 5 cases (16.7%), while the lowest prevalence was seen in children aged 5–10 years, with only 1 case (3.3%). These findings suggest that younger children, particularly those under 5 years of age, are more susceptible to HAdV infection (Table-3).

Table-3: HAdV Prevalence by Age Group

Age Group (years)	Positive n (%)
<1	5 (16.7%)
1–3	15 (50.0%)
3–5	9 (30.0%)
5–10	1 (3.3%)

Feeding Practices among HAdV-positive Children

The table presents the distribution of Human Adenovirus (HAdV) positivity based on feeding behavior among children with URTI. The highest number of HAdV-positive cases was found in children primarily consuming bread (14 cases, 46.7%), followed by those fed with mother's milk (7 cases, 23.3%). Children who consumed cow milk and those taking a combination of bread and cow milk each accounted for 4 cases (13.3%), while only 1 case (3.3%) was observed among formula-fed children. This indicates that children on less nutritious or mixed diets may have a higher risk of HAdV infection (Table-4).

Table-4: Feeding Practices among HAdV-positive Children

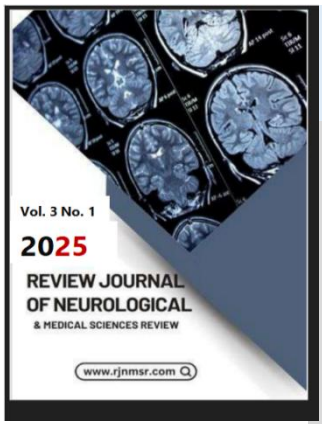
Feeding Behaviour	Positive n (%)
Mother Milk	7 (23.3%)
Formula Milk	1 (3.3%)
Cow Milk	4 (13.3%)
Bread	14 (46.7%)
Bread + Cow Milk	4 (13.3%)

Clinical Symptoms in HAdV-positive Patients

Among the 30 HAdV-positive patients, the most prevalent symptoms were runny nose (100%), cough (80%), and fever (76.7%). Statistical significance (p-values) should be calculated using chi-square or Fisher's exact test (**Table-5**).

Table-5: Prevalence of Symptoms among HAdV-positive Children (n = 30)

Symptom	Positive n (%)
Runny Nose	30 (100%)
Cough	24 (80.0%)
Fever	23 (76.7%)



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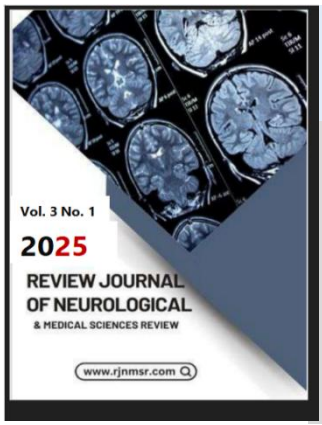
Wheeze	17 (56.7%)
Sneezing	14 (46.7%)
Nasal Obstruction	13 (43.3%)
Sore Throat	13 (43.3%)
Sputum	6 (20.0%)
Throat Swab Positive	6 (20.0%)
Ear Infection	5 (16.7%)
Diarrhea	3 (10.0%)

Discussion

This study is the first to report the prevalence and molecular detection of Human Adenovirus (HAdV) among children with upper respiratory tract infections (URTI) in tertiary care hospitals in Peshawar. HAdV was identified in 32.3% of the children tested, indicating it as a significant viral agent in pediatric URTIs. Globally, URTIs account for 85–88% of acute respiratory infections in children, with the remainder being lower respiratory tract infections (Alaranta et al., 2012). A total of 93 children were included, with 55% males and 44% females. Age distribution showed most were preschool-aged (55%), followed by infants (21%), toddlers (19.35%), and school-aged children (3.22%) as per WHO classification. Feeding patterns showed 39% of children were on bread only, followed by bread + cow milk (18%), cow milk (17%), mother's milk (15%), and formula milk (9.7%). In contrast, higher rates of breastfeeding were reported in studies from Tehran (69%) (Tehran, 2010), Pakistan (65%) (Shahzad, 2009), and Nepal (38%) (Rijal et al., 2011).

URTI symptoms recorded from all patients using a standardized questionnaire showed the most common symptoms were runny nose (91%), fever (83%), and cough (81%). Other symptoms included sneezing (55%), wheeze (51%), nasal obstruction (49%), sore throat (27%), ear infection (17%), and diarrhea (9.7%). These findings align with reports from Ghana, Dar es Salaam, and other regions showing similar symptom profiles (Denno et al., 2014; Athumani, 2010). Children experienced 3–7 URTI episodes annually, slightly below global estimates of 4–9 infections per year (Bloom et al., 2007). Annually, 11–33 million URTI cases occur among children under two years (Bloom et al., 2007). PCR testing revealed 30 children (32.3%) were HAdV-positive. This rate aligns with findings from other countries: Italy (17.9%) (Fabbiani et al., 2009), Brazil (25%) (Bezerra et al., 2011), China (10.5%–20%) (Li et al., 2015), and Korea (23%–54%) (Lynch et al., 2016). In the U.S., prevalence was 35% among military and 3% in civilian populations (Lynch et al., 2016).

Among HAdV-positive cases, 60% were male and 40% female. Age-wise, 16% were infants, 50% toddlers, 30% preschoolers, and 3.33% school-aged, consistent with other studies showing higher prevalence in children under five (Cheng et al., 2007). The most common symptom among HAdV-positive cases was runny nose (100%), followed by cough (80%), fever (76.6%), wheeze (56.6%), sneezing (46.6%), sore throat and nasal



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obstruction (43.3%), with diarrhea being least reported (10%). These symptoms are in line with prior descriptions of HAdV infections, which include persistent high fever, cough, and gastrointestinal symptoms (Cooper et al., 2000; Bezerra et al., 2011; Chen et al., 2004). Antibiotic usage was high: 95% of children with URTI and 100% of HAdV-positive cases received antibiotics. This rate exceeds those reported in Indonesia (Gani et al., 1999), Malaysia (Teng et al., 2004), Saudi Arabia (Irshaid et al., 2004), and the U.S. where one-third of URTI patients were prescribed antibiotics (Hicks, 2010). This highlights the overuse of antibiotics in viral URTIs, which contributes to antimicrobial resistance (Arya et al., 2004).

Conclusion and Recommendations

This study highlights the significant prevalence of Human Adenovirus (HAdV) among children presenting with upper respiratory tract infections (URTI) in tertiary care hospitals in Peshawar, with 30 out of 93 (32.25%) children testing positive by PCR. The findings confirm that HAdV is a major viral pathogen contributing to pediatric URTIs in this region, with most cases occurring mid-year. The infection was more common among children under five years, aligning with global trends. Clinical symptoms such as runny nose, cough, fever, and wheezing were frequently observed among HAdV-positive children, underscoring the virus's potential to cause significant respiratory illness.

Antibiotic overuse remains a critical concern, as 95% of all URTI cases and 100% of HAdV-positive cases received antibiotics despite the viral nature of the infection. This pattern reflects inappropriate prescribing practices that may contribute to the global challenge of antibiotic resistance. Misuse of antibiotics in pediatric viral infections undermines treatment efficacy and endangers public health.

To address these issues, future efforts should focus on molecular surveillance of HAdV and its seasonal patterns in diverse populations. Continued research is essential to understand the virus's epidemiology, co-infection dynamics, and potential complications. There is also a pressing need to develop effective vaccines against HAdV, particularly for young children, to reduce disease burden and associated complications. Additionally, public health interventions should include clinician training and awareness campaigns to promote rational antibiotic use and reduce unnecessary prescriptions in viral URTI cases.

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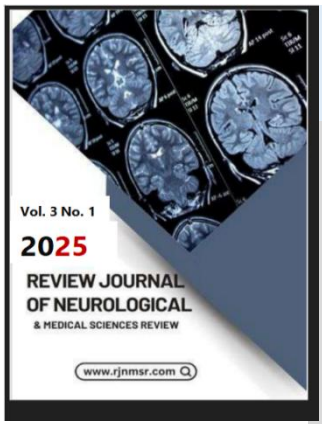

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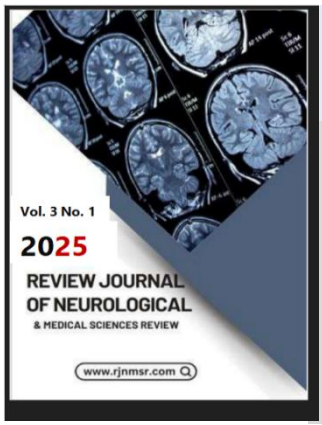

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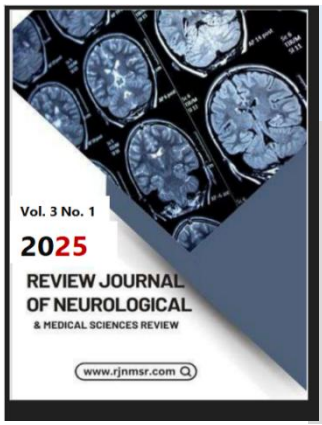

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