VOLUME - 11, ISSUE - 12, DECEMBER - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Pediatrics

A STUDY ON CLINICAL PROFILE AND NON-COVID RESPIRATORY VIRAL INFECTIONS IN A NON-COVID TERTIARY CARE HOSPITAL IN KOLKATA DURING COVID PANDEMIC

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ABSTRACT **Objectives:** To evaluate the clinical picture and viral aetiologies (other than SARS-CoV-2) of acute respiratory tract infections in under- five children during the COVID-19 pandemic. **Methods:** This was a hospital based, prospective, observational and cross-sectional study carried out among under-five children admitted at IPGME & R, Kolkata, satisfying both inclusion and exclusion criteria. During the study period of one and a half year, after taking consent from the parents, clinical data were collected in pre-formed questionnaire and rt-PCR was implemented to detect respiratory viral pathogen. The statistical analysis was done by using Statistica version 8. **Results:** A total of 142 children of mean age 13.18 months with Acute Respiratory Infection (ARI) and COVID RT-PCR negative were included in this study. Passive smoking (p-value 0.023), partially completed vaccination (p-value 0.041), non-exclusive breast-feeding in first 6 months of life (p-value 0.031), history of low birth weight (p-value 0.044) and family history of recent contact of ARI has statistically significant positive correlation with ARI (0.018). Rhinorrhoea was the most common symptom (prevalence 84%). RSV-A was the most common viral pathogen (33.10%). The death was most strongly associated with adenovirus (RR= 7.962; OR= 28.846; 95%CI= 2.795- 297.719). Congestive cardiac failure, secondary bacterial pneumonia, acute otitis media and acute gastroenteritis were the most prevalent complications. **Conclusion:** The results provided aetiology, prevalence, seasonality, and clinical manifestations of upper respiratory tract infections and the association of complications and death with each pathogen during the COVID-19 pandemic. Further studies will detect broader range of viruses for better clinico-virological correlation.

KEYWORDS : Acute Respiratory Infections (ARI), COVID-19 pandemic, rt-PCR.

INTRODUCTION:

Respiratory tract infections (RTIs) such as acute otitis media, sinusitis, bronchitis, and community-acquired pneumonia are a leading cause of infectious disease–related morbidity, hospitalization, and mortality among children worldwide, particularly in low-income countries[1]. Viral respiratory infections are among the most common causes of disease in humans, especially among children and infants, and a major public health problem due to the high prevalence, ease of transmission, and the significant morbidity and mortality associated with these infections[2]. ARIs rank among the top five causes of illness and hospitalisation in children, with high childhood mortality leading to about five million fatalities per year in developing countries in children younger than 5 years of age[2].

After thorough review of available literature, it is seen that robust clinical data is not available in India on the impact of other known respiratory viral pathogen (Respiratory syncytial virus, influenza virus, adenovirus, parainfluenza virus, rhinovirus and human metapneumovirus) causing acute respiratory infections during the COVID-19 pandemic. The devastating nature of the pandemic has drawn the attentions of the public and private sectors of Medical system in our country towards SARS-CoV-2. However, the other respiratory viruses also have their share in the prevalence of acute respiratory infections (ARI) in under-five children during the pandemic. In this study, during the COVID-19 pandemic, the characterisation of the viral spectrum and the pattern of acute respiratory infections (ARI) in under-five children from the Eastern part of India has been aimed at.

The recent increasing use of respiratory pathogen PCR amplification methods in studies of upper respiratory infections has provided new information on the epidemiology of respiratory tract infections and has contributed to a better understanding of the seasonality of these etiologic agents and their association with certain clinical manifestations[3]. This study explores the aetiology, prevalence, seasonality, and clinical manifestations of upper respiratory infections at a tertiary care medical centre using a rapid multiplex PCR respiratory pathogen panel.

AIMS AND OBJECTIVES:

General Objective:

To evaluate the viral aetiologies (other than SARS-CoV-2) of acute respiratory infections in under- five children during the COVID-19 pandemic.

Specific Objectives:

I. To evaluate the clinical picture of acute viral respiratory infections in under-five children during the COVID-19 pandemic.
II. To evaluate the risk factors of acute viral respiratory infections in them.
III. To assess short term outcome with prognostic factors.

MATERIALS AND METHOD:

A hospital based, prospective, observational, cross-sectional study has been performed in the children of ages between 2 months and 5 years, suffering from ARI and satisfying the inclusion and exclusion criteria of this study, admitted in the in-patients' department (IPD) of the Department of Paediatric Medicine, IPGMER & SSKM Hospital, Kolkata, a Tertiary Care Multispecialty Hospital in Kolkata during the study period from April 2020 to December 2021. The data collection was started just after the implementation of lockdown in India (22th March, 2020). Being a prospective observational study we did not go for a formal sample size calculation. However, 142 children were included in the study.

Inclusion criteria:

- Children suffering from acute respiratory tract infection.
- Children aged between 2 months to 5 years.
- Parent willing to provide written informed consent.

Exclusion criteria:

- Children suffering from suspected bacterial infection.
- Children having any chronic illness or disability.
- Children suffering from recurrent pneumonia.
- Children having HIV infection.
- Children with severe malnutrition.
- Children hospitalized in last one month.
- Children having any congenital malformation.
- COVID-19 positive cases.

After obtaining ethical clearance from the Institutional Ethics Committee, this study was conducted among the study population after taking written informed consent from the parents/guardian. The study place was a non-COVID hospital, so following admission of the ARI patients, we used to perform COVID-19 RT-PCR test. Those patients who were tested negative were included in the study. Each study participant was properly evaluated and treated for the present illness and at the same time, a predesigned and pretested questionnaire was used for data collection. Oropharyngeal swabs were obtained from the participants from the posterior wall of oropharynx and put into the vial containing 1 mL of viral transport medium (VTM). The collected swabs were transported in ice-pack within 1 hour to the regional VRDL, ICMR-NICED, Kolkata, where viral nucleic acids were extracted by using Viral RNA/DNA Mini Kit. The extracted nucleic acids were then subjected to real time PCR for detection of respiratory viruses. The results were analysed and the test results helped in the treatment of these patients.

Statistical analysis: For statistical analysis, data were entered into a Microsoft excel spreadsheet and then analysed by *Statistica* version 8 and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. A chi-squared test (2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. If the calculated p-value was below the threshold chosen for statistical significance (=0.05), then the null hypothesis was rejected in favour of the alternative hypothesis. P-value ≤ 0.05 was considered as statistically significant.

RESULTS:

The study population comprised of 142 cases among which 73 (51.4%) were male and 69 (48.6%) were female. The mean and median ages of the participants were 13.18 months and 6.0 months respectively. Among total 142 cases, 106 patients (74.65%) were infants; 126 patients (88.73%) were discharged after recovery, but 16 patients died (11.27%).

In the present study majority of the cases (total 83 in number, 58.45%) occurred in winter, which was followed by autumn (27 patients, 19.01%), spring (15 patients, 10.56%), rainy season (10 patients, 7.04%) and summer (7 patients, 4.93%) respectively.

From this study, it was found that passive smoking (p-value 0.023), partially completed vaccination as per National Immunisation Schedule (p-value 0.041), non-exclusive breast-feeding in first 6 months of life (p-value 0.031), history of low birth weight (p-value 0.044) and family history of recent contact of ARI (p-value 0.018) has statistically significant positive correlation with ARI (Table I).

Table I: Association of risk factors with ARI

		Discharged [n(%)]	Death [n(%)]	p-value
Gender	Male	64 (50.79%)	9 (56.25%)	0.793
	Female	62 (49.21%)	7 (43.75%)	
Passive smoking	Yes	95 (75.40%)	16 (100.00%)	0.023
	No	31 (24.60%)	0 (00.00%)	
Complete vaccination	Yes	95 (75.39%)	8 (50.00%)	0.041
	No	31 (24.61%)	8 (50.00%)	
EBF	Yes	75 (59.52%)	5 (31.25%)	0.031
	No	51 (40.48%)	11 (68.75%)	
Family history of recent contact	Yes	21 (16.67%)	7 (43.75%)	0.018
	No	105 (83.33%)	9 (56.25%)	
Low birth weight	Yes	60 (47.62%)	4 (25.00%)	0.044
	No	66 (52.38%)	12 (75.00%)	

A total of 40 participants had their weight for height below 15th percentile in WHO weight for height growth chart. A positive correlation between acute malnutrition and ARI was found to be present (p value 0.023). A total of 13 patients had their height for age below 15th percentile in WHO weight for height growth chart. A positive correlation between chronic malnutrition and ARI was also found to be present (p value 0.015).

Rhinorrhoea (83.80%), Cough (69.71%) and fever (69.71%) were the most common symptoms among the study population. Signs of severe acute respiratory illness (refusal to feed, chest indrawing, grunting, vomiting what consumed, convulsions) were present in 73 patients (51.41%).

Among total 142 cases, 50 patients were tested negative for any viral pathogen. Among the positive tests, RSV-A was the most common pathogen (47 cases, 33.10%), followed by rhinovirus (9 cases, 6.34%) and human parainfluenza 1 virus (7 cases, 4.93%) (Table II). In nine positive cases (6.34%) more than one respiratory viruses were detected.

Table II: Aetiology by RT-PCR

	Discharge	Death	Totals
None	49	1	50
Column %	38.89%	6.25%	35.21%
RSV-A	43	4	47
Column %	34.13%	25.00%	33.10%
RSV-A + Rhino	2	1	3
Column %	1.59%	6.25%	2.11%
RSV-B	3	0	3
Column %	2.38%	0.00%	2.11%
RSV-A + Parainfluenza 1 + Parainfluenza 2	1	0	1
Column %	0.79%	0.00%	0.70%
Rhino	7	2	9
Column %	5.56%	12.50%	6.34%
Adeno	1	3	4
Column %	0.79%	18.75%	2.82%
Metapneumovirus	4	1	5
Column %	3.17%	6.25%	3.52%

Influenza A	1	1	2
Column %	0.79%	6.25%	1.41%
Parainfluenza 1	6	1	7
Column %	4.76%	6.25%	4.93%
Parainfluenza 1 + arainfluenza 2	1	1	2
Column %	0.79%	6.25%	1.41%
Parainfluenza 2	1	0	1
Column %	0.79%	0.00%	0.70%
Parainfluenza 3	4	0	4
Column %	3.17%	0.00%	2.82%
Parainfluenza 4	1	0	1
Column %	0.79%	0.00%	0.70%
Parainfluenza 3 + Parainfluenza 4	2	1	3
Column %	1.59%	6.25%	2.11%
Totals	126	16	142

Among total 92 cases of viral causes of ARI, death occurred in 15 cases (16.30%). The death was most strongly associated with adenovirus [Relative Risk (RR)= 7.961; Odds Ratio (OR)= 28.846; 95%Confidence Interval (CI)= 2.795- 297.719], followed by Influenza A virus (RR= 4.667; OR= 8.333; CI= 0.495- 140.245), followed by combined viral infections (RR= 3.410; OR= 4.615; 95%CI= 1.030- 20.673), then rhinovirus (RR= 2.111; OR= 2.429; 95%CI= 0.459- 12.852), then metapneumovirus (RR= 1.827; OR= 2.033; 95%CI= 0.213- 19.408), and then parainfluenza 1 virus (RR= 1.286; OR= 1.333; 95%CI= 0.150- 11.842). Death was least strongly associated with RSV A (RR= 0.674; OR= 0.643; 95%CI= 0.196- 2.115).

Among total 65 cases of viral causes of ARI in infants, death occurred in 10 cases (15.38%). The death in infants was most strongly associated with adenovirus infection (RR= 5.778; OR= 10.556; 95%CI= 0.608- 183.379) and influenza-A virus (RR= 5.778; OR= 10.556; 95%CI= 0.608- 183.379), followed by metapneumovirus (RR= 3.815, OR= 5.222, 95%CI= 0.430- 63.367), then mixed viral infections (RR= 3.536; OR= 4.55; 95%CI= 0.758- 27.309) and then rhinovirus (RR= 1.852; OR= 2.022; 95%CI= 0.212- 19.257). The death of infants was least strongly associated with RSV-A (RR= 0.904; OR= 0.894; 95%CI= 0.237- 3.375).

The viral acute respiratory infections was complicated by congestive cardiac failure (n=10), secondary bacterial pneumonia (n=13), acute otitis media (n=6), acute gastroenteritis (n=6), pleural effusion (n=1) and meningitis (n=1).

DISCUSSION:

The coronavirus pandemic was at its peak in between late-March and mid-September (the first wave) in 2020 and again in early-April to late-August in 2021(the second wave) in India, i.e. during summer, rainy season and autumn. During this time, 44 samples were tested, 21 cases were positive for any respiratory virus (47.73%). During winter and spring season, 98 samples were tested, 71 cases were positive for any respiratory virus (72.45%). The galloping inflation of COVID-19 positivity rates, the Government's policies to control the pandemic situation and common people's hygiene practices and social distancing may influenced the lower positivity rates of other respiratory viruses during SARS-CoV pandemic waves.

Passive smoking (p-value 0.023), partially completed vaccination (p-value 0.041), non-exclusive breast-feeding in first 6 months of life (p-value 0.031), history of low birth weight (p-value 0.044) and family history of recent contact of ARI has statistically significant positive correlation with ARI (0.018) similar to the studies of[4,5,6]. In a descriptive cross-sectional study by Pushpa Thapa et al[4], it was seen that non-exclusively breastfed children with presence of anyone smoking at their house and smoking in the presence of children had higher chance of ARI; nevertheless, this remained among the exclusively breastfed ones.

The acute and chronic malnutrition had significant correlation with acute respiratory infections in this study (p-value 0.023 for acute malnutrition and 0.015 for chronic malnutrition). The study by Awoke Keleb et al[6] also showed significant association between childhood pneumonia and acute malnutrition (AOR = 2.43, 95%CI: 1.18-5.04). The study by Abhishek Arun et al[5] also found a significant association between ARI and nutritional status (p <0.001).

The overall positivity in this study is 64.79% with a coinfection rate of 6.34% versus in the study done by Bharti Malhotra et al[7] where overall positivity was 72.9% with a co-infection rate of 19.5%. The RSV-A (33.10%) was the most common virus detected in this study, followed by rhinovirus (6.34%) and parainfluenza 1 virus (4.92%). In a study by Yeolekar L. R. et al[8], the most common was respiratory syncytial virus (RSV) in 100 (26%) patients, followed by influenza viruses in 21 (5.4%), parainfluenza in 8 (2.07%), adenovirus in 3 (0.8%). One patient had mixed infection of RSV and adenovirus. In the study of Broor S et al[9] RSV was detected in 61, parainfluenza 3 in 22, parainfluenza 2 in 17, human metapneumovirus in 11, parainfluenza 1 in 10 and influenza A in 9 children. RSV was the most common pathogen (63.6%), followed by rhinovirus (39%) found in a study by Nascimento M. S., de Souza A. V. et al[10]. Christy S. Stover and Christine M. Litwin[11], in their study found that Rhinovirus/enterovirus (Rhino/Entero) infections were the most prevalent (25.4%) followed by respiratory syncytial virus (RSV) (13.6%) and influenza A (6.2%). In an observational cross-sectional study by Mishra P et al[12] RSV was found to be most prevalent viral pathogen (24.6%) followed by rhinovirus (21.8). In another cross-sectional study by Hassan D A et al, Rhinovirus (32.7) was the most prevalent pathogen, followed respectively by RSV (20.4), adenovirus (6.3), HPIV1 (5.9).

The death was most strongly associated with adenovirus (RR= 7.962; OR= 28.846; 95%CI= 2.795- 297.719) and least strongly associated with RSV A (RR= 0.674; OR= 0.643; 95%CI= 0.196- 2.115) in the study population. The death in infants was most strongly associated with adenovirus infection (RR= 5.778; OR= 10.556; 95%CI= 0.608- 183.379) and influenza-A virus (RR= 5.778; OR= 10.556; 95%CI= 0.608- 183.379), it was least strongly associated with RSV-A (RR= 0.904; OR= 0.894; 95%CI= 0.237- 3.375). After thorough literature review, no such study was found mentioning statistical association of deaths (in terms of RR, OR, 95%CI) in infants by specific viruses.

The development of congestive cardiac failure (n=10) had statistically significant correlation with rhinovirus infection (p value 0.003). Secondary bacterial pneumonia development (n=13) had positive correlation with adenovirus (p value 0.011) and metapneumovirus (p value 0.039) infection. Acute otitis media (n=6) development had positive correlation with RSV-A (p value 0.0003), parainfluenza 1 (p value 0.003) and mixed viral infections (p value 0.013).Acute gastroenteritis (n=6) had positive correlation with parainfluenza 3 (p value 0.036) and mixed viral infections (p value 0.006).

CONCLUSION:

The present results provided preliminary understanding of the viral agents other than SARS-CoV associated with severe acute respiratory infection (SARI) during COVID-19 pandemic. This study also found incomplete immunisation, non-exclusively breast feeding, family history of recent ARI, passive smoking, low birth weight, malnutrition as significant risk factors for ARI in under-fives. The outcome of the study in terms of death and complications has been analysed in the present study. The death was most strongly associated with

adenovirus infection and least strongly associated with RSV A, in under-5 children with ARI as well as in infants. The association of death with each pathogen in under-5 children, particularly the association of death of infants with each pathogen is a unique part of this study. The association of complications with each virus has also been analysed in terms of statistical significance. However, there is a need for conducting further studies to detect broader range of viruses and other fastidious organisms, to undertake detailed clinical work up for better clinico-virological correlation.

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