Research Article

Disease Burden of Virus-associated Lower Respiratory Tract Infections among Hospitalized Children Under Five Years of Age in Sarawak

Jakie Ting [1, 2], Sing-Ling Kong [3], Tiing-Tiing Chua [2], Tiana Ti [3], Jane K. Fieldhouse [4, 5], King-Ching Hii [3], Gregory C. Gray [4, 5, 6, 7], Teck-Hock Toh [1, 2, 8]

Author's Affiliation:
1- Faculty of Medicine, SEGi University, Kota Damansara, Selangor, Malaysia
2- Clinical Research Center, Sibu Hospital, Ministry of Health Malaysia, Sibu, Sarawak, Malaysia
3- Department of Paediatrics, Kapit Hospital, Ministry of Health Malaysia, Kapit, Sarawak, Malaysia
4- Duke Global Health Institute, Duke University, Durham, North Carolina, USA
5- Division of Infectious Diseases, Duke University School of Medicine, Durham, North Carolina, USA
6- Emerging Infectious Disease Program, Duke-NUS Medical School, Singapore
7- Global Health Center, Duke Kunshan University, Kunshan, China
8- Department of Paediatrics, Sibu Hospital, Ministry of Health Malaysia, Sibu, Sarawak, Malaysia

Correspondence:
Teck-Hock Toh, E-mail: tohth@moh.gov.my

Received on: 02-Apr-2021 Accepted for Publication: 10-Jun-2021

ABSTRACT

Background: Lower respiratory tract infections (LRTI) have a great impact upon young children globally, with high mortality rates. We studied the disease burden of virus-associated LRTI among hospitalized young children in Central Sarawak.

Methods: This is a cross-sectional, observational study of under-five children recruited between June 2017 and May 2018 in Sibu and Kapit Hospitals. We reviewed medical records to compare the disease burden among children with nasopharyngeal swab that were positive by molecular assays for respiratory syncytial virus (RSV), Adenoviruses (AdV), Coronaviruses, Enteroviruses, Influenza or Para influenza viruses.

Results: A total of 196 children with LRTI (mean age: 1.34 +/- 1.08 years) were identified. RSV was the commonest virus detected (54.1%), followed by AdV (24.0%). Compared to the others, AdV-LRTI had a statistically significant longer length of stay (10.1 days vs 7.0 days), duration for intravenous hydration (33.8 hours vs. 17.0 hours), as well as nebulization using saline (128.4 hours vs. 66.3 hours) and salbutamol (151.5 hours vs. 111.32 hours). More children with AdV infection were treated with steroids (23.4%, OR= 7.3, 95% CI: 2.52, 21.01), magnesium sulphate (46.8%, OR= 2.7, 95% CI: 1.35, 5.27), high flow nasal cannula (48.9%, OR= 2.3, 95% CI: 1.17, 4.48), being intubated (10.6%, OR= 5.8, 95% CI: 1.33, 25.25) and received antibiotics (93.6%, OR= 4.0, 95% CI: 1.17, 13.77) than children with other etiologies.

Conclusion: Among under-five children with LRTI, RSV was the most prevalent viral etiological cause, but AdV infection was associated with a higher disease burden by several metrics.

Keywords: Disease burden, hospitalization, lowers respiratory tract infection, pediatrics, respiratory viral infection

INTRODUCTION

For more than a decade, lower respiratory tract infections (LRTI) have been the deadliest communicable diseases worldwide with more than four million deaths annually. [1] Children under five years of age are disproportionately affected; in 2017, LRTI caused 808,694 deaths worldwide in under-five children. [2] In Malaysia, LRTI caused 3.8% of all deaths among the under-five population in 2016. [3]

Etiology and clinical presentation of LRTI varies among individuals cross the globe. Viruses such as Respiratory Syncytial Virus (RSV), Influenza virus (Flu), Parainfluenza virus (PIV) and Adenovirus (AdV) are frequent causes of LRTI and responsible for the majority of LRTI-related hospitalizations.[4, 5] Among these viruses, RSV is the most prevalent respiratory pathogen detected in young children with peak activity during the end of

the year (September to December) in the northern hemisphere.[6] Children hospitalized with LRTI often present with cough, fever, and rapid breathing, and consequently often have reduced energy as well as reduction in fluids intake and feeding. Treatment for LRTI ranges from symptomatic support and invasive ventilation to antimicrobial therapy. However, in the absence of the diagnostic and prognostic tools to differentiate between viral and bacterial LRTI, antimicrobials are often inappropriately and/or empirically used and mismanaged. [7, 8] Thus, it is important to understand what pathogens are circulating among patients and disease burden they cause.

Currently, there is a paucity of data regarding the disease burden of viral causes of pneumonia among children less than five years of age in Sarawak, on the northern central coast of Borneo. Metrics for disease burden include duration of various presenting illness and requirement of different inpatient treatments, as well as duration of hospitalization, and etiological causes of LRTI in under-five children. In this study, we aimed to determine the viral etiology and disease burden of LRTI among these children in Sarawak, as well as disease burden differences between children infected by different viruses. We also studied the differences of disease burden for children with a single viral infection versus co-infections.

METHODS

Study Design

We conducted a cross-sectional case record review study using the secondary data of a year-long cross-sectional surveillance study.

Setting

The initial study was conducted between June 2017 and May 2018 at Sibu and Kapit Hospitals for viral etiological causes.[9]

Participants

Definition of the LRTI was described in details in the previous study publication.[9] A medical officer would have evaluated eligible subjects for inclusion and exclusion criteria, including confirmation by chest radiography within 72 hours of hospitalization. We recruited all the children under five years of age with a complete medical record who had a nasopharyngeal swab that was positive by real-time polymerase chain reaction (PCR) or real-time reverse transcription PCR for RSV, Flu, PIV, AdV, EV and/or CoV. The laboratory assays used to examine the nasopharyngeal swabs for viral agents were described in the previous study publication. [9]

Variables and Data Collection

We reviewed the demographic and laboratory data as well as medical records of all children with viral infections. We studied the disease burden, including the length of stay (LOS), duration of symptoms (fever, activity and feeding status) as well as the duration of treatment [intravenous (IV) fluids rehydration, ventilation support, nebulization and antibiotics usage].

Statistical Analysis

We used Statistical Package for Social Sciences software (SPSS) version 22 to analyze the data. Demographic and laboratory data were examined using descriptive statistics. We compared the categorical variables by using chi-square or Fisher's exact tests as appropriate. We used an independent t-test to compare the mean between groups. The significance level was set at 0.05 and 95% confidence intervals (CIs) were calculated.

The initial study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-12-16-10787). Written informed consent was obtained from all parents or caregivers; and the study was conducted according to the Declaration of Helsinki. We report according to the standard set by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[10]

RESULTS

During the study period, 385 children under five years of age provided a nasopharyngeal swab specimen, of which, 222 (57.7%) were positive for one or more viruses. Among the children who were positive for viral infection, 196 (88.3%) had complete medical records and were recruited into the secondary study, 115 (58.7%) of whom were hospitalized at Sibu Hospital and 81 (41.3%) at Kapit Hospital. Table 1 summarizes the basic demographic data of the children, as well as the length of stay (LOS), duration of fever, days being less active and days of reduced feeding. The mean LOS for the cohort was 7.7 (SD: 4.20) days, with 13 (6.6%) of them stayed for more than 2 weeks (max = 21 days). There was no death during the admission among the children studied in this cohort, and all of them were discharged well.

Table 1. Demographic data, clinical symptoms and treatment of children under five years of age with lower respiratory tract infection

	Frequency (%) n=196	Mean (SD)
Age (years)	-	1.3 (1.08)
Gender		
Male	105 (53.6)	-
Female	91 (46.4)	-
LOS (days)	-	7.7 (4.20)
Fever (days)	-	4.3 (15.46)
Less active (days)	-	2.8 (3.31)
Reduced feeding (days)	-	3.6 (3.70)
IV Hydration (hours)	109 (55.6)	21.1 (31.03)
NPO2 (hours)	179 (91.3)	98.0 (122.41)
Nebulization (hours)		
Salbutamol	165 (84.2)	121.1 (99.62)
Saline	136 (69.4)	81.3 (90.46)
Ipratropium bromide	61 (31.1)	17.6 (43.53)
Steroids		-
No	179 (91.3)	
Yes	17 (8.7)	
IV MgSO4		-
No	137 (69.9)	
Yes	59 (30.1)	
SC Terbutaline		-
No	160 (81.6)	
Yes	36 (18.4)	
HFNC		-
No	129 (65.8)	
Yes	67 (34.2)	
Intubation		-
No	188 (95.9)	
Yes	8 (4.1)	
Antibiotics (types)		-
0	35 (17.9)	
1-3	151 (77.0)	
4-6	10 (5.1)	

SD= standard deviation, LOS= length of stay, IV= intravenous, NPO2= nasal prong oxygen, MgSO4= magnesium sulphate, SC= subcutaneous, HFNC= high flow nasal cannula

The analysis of treatments (Table 1) shows that children with LRTI required a significant number of treatments with IV hydration, nasal prong oxygen supply, salbutamol, saline and ipratropium bromide nebulization with the

mean durations of 21.1 (±31.03), 98.0 (±122.41), 121.1 (± 99.62), 81.3 (± 90.46) and 17.6 (± 43.53) hours respectively. While there were 17 children (8.7%) received steroids, 30.1% (n = 59) received IV magnesium sulphate (MgSO4) and 18.4% (n = 36) received subcutaneous terbutaline treatment. One third (n = 67, 34.2%) of children received high flow nasal cannula oxygen (HFNC) treatment. Eight children (4.1%) were admitted to pediatric intensive care unit and were ventilated. The majority of children (n = 151, 77.0%) received one to three types of antibiotics during hospitalization, while 5.1% (n = 10) of children were treated with four to six types of antibiotics during the hospital stay.

Table 2. Comparison of disease burden between Adenovirus (AdV) and non-Adenovirus (non-AdV) infection

	Mean (SD)		Mean Difference (95% CI)	*t* statistic (*df*)	*P* value*
	AdV	Non-AdV			
Age (years)	1.0 (0.67)	1.4 (1.16)	-0.4 (-0.66, -0.12)	-2.83 (136.15)	0.005
LOS (days)	10.1 (4.12)	7.0 (3.94)	3.2 (1.85, 4.48)	4.74 (194)	<0.001
Fever (days)	7.4 (5.05)	6.2 (3.58)	1.2 (-0.37, 2.84)	1.54 (59.87)	0.129
Less active (days)	3.5 (4.10)	2.6 (3.02)	0.9 (-0.44, 2.23)	1.35 (57.63)	0.183
Reduced feeding (days)	3.9 (4.57)	3.5 (3.40)	0.3 (-1.13, 1.82)	0.47 (59.48)	0.643
IV Hydration (hours)	33.8 (40.42)	17.0 (26.26)	16.8 (4.18, 29.32)	2.67 (58.92)	0.010
Nebulization (hours)					
Saline	128.4 (97.69)	66.3 (82.89)	62.1 (30.56, 93.62)	3.93 (68.47)	<0.001
Salbutamol	151.5 (95.61)	111.32 (99.23)	40.1 (7.56, 72.70)	2.43 (190)	0.016
Ipratropium bromide	24.02 (44.27)	15.62 (43.26)	8.4 (-6.21, 23.02)	1.134 (190)	0.258
NPO_2 (days)	119.7 (78.23)	91.2 (132.83)	28.4 (-12.30, 69.17)	1.38 (190)	0.170

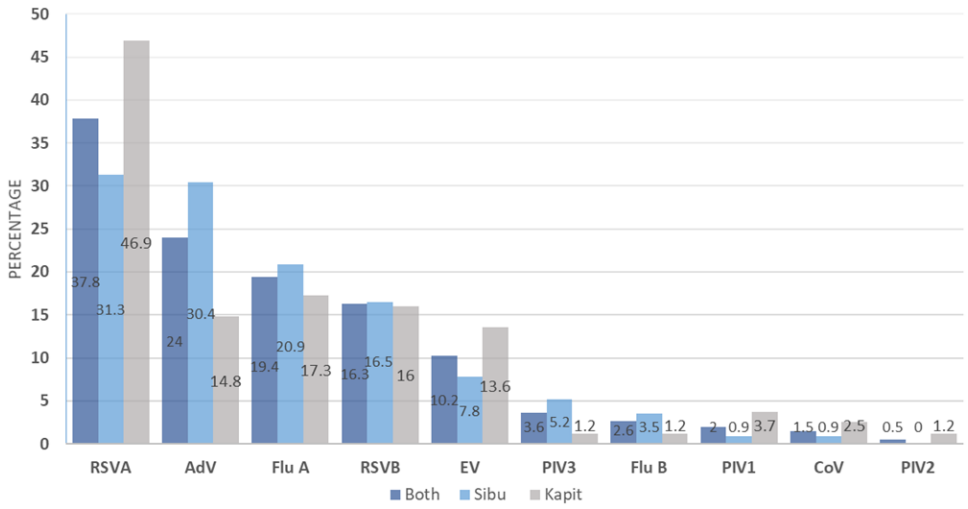
	Frequency (%)		OR (95% CI)	$\chi 2$ statistic (df)	P value†
	AdV (n=47)	Non-AdV (n=149)			
Steroids	11 (23.4)	6 (4.0)	7.3 (2.52, 21.01)	-	<0.001‡
IV MgSO4	22 (46.8)	37 (24.8)	2.7 (1.35, 5.27)	7.19 (1)	0.007
SC Terbutaline	10 (21.3)	26 (17.4)	1.3 (0.57, 2.89)	0.140 (1)	0.708
HFNC	23 (48.9)	44 (29.5)	2.3 (1.17, 4.48)	5.15 (1)	0.023
Intubation	5 (10.6)	3 (2.0)	5.8 (1.33, 25.25)	-	0.020‡
Antibiotics	44 (93.6)	117 (78.5)	4.0 (1.17, 13.77)	4.57 (1)	0.033

SD= standard deviation, LOS= length of stay, IV= intravenous, NPO2= nasal prong oxygen
IV= intravenous, MgSO4= magnesium sulphate, SC= subcutaneous, HFNC= high flow nasal cannula
***Independent t-test, equal variance assumed**
†Yates' chi-square test
‡Fisher exact test

Among all respiratory viruses identified, RSV was the most common virus detected with the prevalence of 54.1% (RSV A = 74, 37.8%; RSV B = 32, 16.3%), followed by AdV (n = 47, 24.0%), Flu virus (Flu A = 38, 19.4%; Flu B = 5, 2.6%), EV (n = 20, 10.2%), PIV (PIV1 = 4, 2.0%; PIV2 = 1, 0.5%) and coronavirus (n = 3, 1.5%). However, Flu virus was more prevalent than AdV in Kapit Hospital (n = 15, 18.5% vs 12, 14.8%) compared to Sibu Hospital (n = 28, 24.4% vs n = 35, 30.4%). (Figure 1)

When we compared the burden of disease in children infected with the different viruses, children with RSV infection had shorter period of fever (1.6 days, 95% CI: 0.49, 2.80, t statistic (df) = -2.82 (150.18), p = 0.005), but otherwise no statistical difference in symptoms or required treatment compared to those with infection

Figure 1. Prevalence of respiratory virus detections among children under five years of age with lower respiratory tract infections. RSV= respiratory syncytial virus, AdV= adenovirus, Flu= influenza, EV= enterovirus, PIV= parainfluenza virus, CoV= coronavirus.



caused by non-RSV viruses (Supplementary Table 1). By comparing AdV and non-AdV infection (Table 2), children with AdV infection were significantly younger (0.4 years, 95% CI: 0.12, 0.66, t statistic (df) = -2.83 (136.15), p = 0.005) and more likely to have longer LOS (3.2 days, 95% CI: 1.85, 4.48, t statistic (df) = 4.74 (194.00), p < 0.001), duration of IV hydration (16.8 hours, 95% CI: 4.18, 29.32, t statistic (df) = 2.67 (58.92), p = 0.010) as well as duration for nebulization using saline (62.1 hours, 95% CI: 30.56, 93.62, t statistic (df) = 3.93 (68.47), p < 0.001) and salbutamol (40.1 hours, 95% CI: 7.56, 72.70, t statistic (df) = 2.43 (190.00), p = 0.016). It was also clear that more children with AdV infection were treated with steroid (n=11, 23.4%, OR: 7.3, 95%CI: 2.52, 21.01, p < 0.001), MgSO4 (n=22, 46.8%, OR = 2.7, 95% CI: 1.35, 5.27, □2 = 7.19, p = 0.007), HFNC (n=23, 48.9%, OR = 2.3, 95% CI: 1.17, 4.48, □2 = 5.15, p = 0.023), being intubated (n=5, 10.6%, OR = 5.8, 95% CI: 1.33, 25.25, p = 0.020) and treated with antibiotics (n=44, 93.6%, OR = 4.0, □2 = 4.57, p = 0.033).

Children with influenza infection were more likely to be older (0.4 years, 95% CI: 0.07, 0.80, t statistic (df) = 2.37 (194.00), p = 0.019) and have a prolonged fever (2.2 days, 95% CI: 0.83, 3.54, t statistic (df) = 3.17 (190.00), p = 0.002), while requiring shorter duration of saline (36.9 hours, 95% CI: 12.70, 61.09, t statistic (df) = -3.02 (102.76), p = 0.003) and ipratropium bromide nebulization (13.3 hours, 95% CI: 2.83, 23.73, t statistic (df) = -2.50 (138.76), p = 0.013) compared to those with non-influenza infection (Table 3). Children with flu infection were also negatively associated with MgSO4 treatment (n=6, 14.3%, OR = 0.3, 95% CI: 0.13, 0.80, □2 = 5.44, p = 0.020). Children with EV infection had a shorter duration of fever (1.9 days, 95% CI: 0.01, 3.80, t statistic (df) = -1.98 (190.00), p = 0.049) and reduced feeding (2.2 days, 95% CI: 1.03, 3.43, t statistic (df) = -3.79 (32.11), p = 0.001). There was no significant difference between EV and non-EV infection in term of duration of treatment (Supplementary Table 2).

Of the total 196 children with LRTI, 34 (17.3%) had respiratory viral co-infection, of which one of these children was co-infected with three types of respiratory viruses (Table 4). Among all the respiratory viruses we identified, PIV1 had the highest co-infection rate although the number were small (n=3, 75.0%, OR = 15.6, 95%CI: 1.57, 154.72, p = 0.017). The other viruses that had significant co-infection rate were AdV (n = 23, 48.9%, OR = 12.0, 95%CI: 5.20, 27.82, □2 = 40.18, p < 0.001); EV (n = 9, 45.0%, OR = 4.9, 95%CI: 1.86, 13.13, p = 0.002); and RSV B (n = 12, 37.5%, OR = 3.9, 95%CI: 1.66, 9.01, □2 = 9.22, p = 0.002). . There was no significant difference in the symptoms and treatments provided, when we compared the disease burden between children with co-infections versus single infection (Supplementary Table 3). Nevertheless, children with co-infection were more likely to be intubated during hospitalization (11.8%, OR = 5.3, 95% CI: 1.25, 22.23, p = 0.032).

Table 3. Comparison of disease burden between Influenza (Flu) and non-Influenza (non-Flu) infection

	Mean (SD)		Mean Difference (95% CI)	t statistic (df)	P value*
	Flu	Non-Flu			
Age (years)	1.7 (1.38)	1.2 (0.96)	0.4 (0.07, 0.80)	2.37 (194)	0.019
LOS (days)	6.8 (4.29)	8.0 (4.15)	-1.1 (-2.57, 0.30)	-1.56 (194)	0.121
Fever (days)	8.2 (3.42)	6.0 (4.03)	2.2 (0.83, 3.54)	3.17 (190)	0.002
Less active (days)	3.2 (3.05)	2.7 (3.38)	0.6 (-0.60,1.70)	0.94 (190)	0.346
Reduced feeding (days)	4.5 (3.22)	3.4 (3.79)	1.2 (-0.09, 2.44)	1.83 (192)	0.068
IV Hydration (hours)	21.1 (32.47)	21.1 (25.28)	0 (-10.82, 10.76)	-0.01 (192)	0.996
Nebulization (hours)					
Saline	89.3 (95.67)	52.4 (61.00)	-36.9 (-61.09, -12.70)	-3.02 (102.76)	0.003
Salbutamol	95.4 (110.60)	127.7 (95.91)	-32.4 (-67.39, 2.68)	-1.82 (190)	0.070
Ipratropium bromide	7.21 (23.28)	20.5 (47.33)	-13.3 (-23.73, -2.83)	-2.50 (138.76)	0.013
NPO2 (days)	95.45 (191.95)	98.8 (95.23)	-3.3 (-45.56, 38.96)	-0.15 (190)	0.878
	Frequency (%)		**OR (95% CI)**	**χ2 statistic (df)**	**P value†**
	Flu (n=42)	Non-Flu (n=154)			
Steroids	1 (2.4)	16 (10.4)	0.2 (0.03, 1.63)	-	0.128‡
IV MgSO4	6 (14.3)	53 (34.4)	0.3 (0.13, 0.80)	5.44 (1)	0.020
SC Terbutaline	3 (7.1)	33 (21.4)	0.3 (0.08, 0.97)	3.59 (1)	0.058
HFNC	9 (21.4)	58 (37.7)	0.45 (0.20, 1.01)	3.18 (1)	0.075
Intubation	1 (2.4)	7 (4.5)	0.5 (0.06, 4.28)	-	1.000‡
Antibiotic	37 (88.1)	124 (80.5)	1.8 (0.65, 4.94)	0.83 (1)	0.363

SD= standard deviation, LOS= length of stay, IV= intravenous, NPO2= nasal prong oxygen, MgSO4= magnesium sulphate, HFNC= high flow nasal cannula
***Independent t-test, equal variance assumed**
†Yates' chi-square test
‡Fisher exact test

Table 4. Distribution of respiratory viral co-infection among children under five years of age with lower respiratory tract infection and odd ratio for having co-infection

Viral Type	Co-infection vs Single Infection				
	Frequency (%)		OR (95%CI)	χ2 statistic (df)	P value†
	Co-infection (n=34)	Single infection (n=162)			
AdV	23 (67.6)	24 (14.8)	12.0 (5.20, 27.82)	40.18 (1)	<0.001
RSV A	13 (38.2)	61 (37.7)	1.0 (0.48, 2.19)	0.00 (1)	1.000
RSV B	12 (35.3)	20 (12.3)	3.9 (1.66, 9.01)	9.22 (1)	0.002
EV	9 (26.5)	11 (6.8)	4.9 (1.86, 13.13)	-	0.002‡
Flu A	6 (17.6)	32 (19.8)	0.9 (0.33, 2.28)	0.00 (1)	0.965
PIV 1	3 (8.8)	1 (0.6)	15.6 (1.57, 154.72)	-	0.017‡
Flu B	2 (5.9)	3 (1.9)	3.3 (0.53, 20.63)	-	0.208‡
PIV 3	1 (2.9)	6 (3.7)	0.8 (0.09, 6.76)	-	1.000‡
CoV	0 (0.0)	3 (1.9)	-	-	1.000‡
PIV 2	0 (0.0)	1 (0.6)	-	-	1.000‡

RSV= respiratory syncytial virus, AdV= adenovirus, Flu= influenza virus, EV= enterovirus, PIV= parainfluenza virus, CoV= coronavirus
†Yates' chi-square test
‡Fisher exact test

DISCUSSION

Our study showed that RSV accounted more than half of the viral causes of LRTI among the children under five years of age in Sibu and Kapit Hospitals, followed by about one-fifth each by AdV and Flu virus. These

findings are consistent with the existing literature; RSV is understood to be the primary pathogen that causes LRTI in under-five children globally, accounting for 3.2 million hospitalizations and 59,600 in-hospital mortality in 2015.[11]

In this study, LRTI with different viral etiologies was found to result in different disease burdens among under-five children in terms of clinical presentation and treatment requirements. These differences may be due to different pathogenesis of the viruses and the immune responses they induce.[12] Our study showed that children with AdV were 4.8 months younger whereas those with Flu virus were 4.8 months older. These findings are consistent with studies from other countries. [13, 14, 15]

Our findings were in agreement with other studies, which showed that children with AdV had LOS of about 10 days and had more severe disease burden, including the needs for nebulization, oxygen therapy and intubation.[13] Nevertheless, other studies have suggested children with AdV are less likely to develop lower respiratory illness.[14] The discrepancy between those reports and our findings could be explained by distinct AdV serotypes among the children. It is known that several AdV serotypes such as serotypes 3 and 7 were involved in outbreak and caused severe disease burden. [14, 15] Our team had successfully sequenced 25 AdV-positive specimens from these under-five population and 56% of them were detected as AdV type 7.[16] This suggested that children with AdV type 7 infection might result in more severe burden of disease than other viral infections analyzed in our study. A study in Malaysia on AdV also revealed that AdV type 7 was the most common serotype circulating in children and that severe respiratory illness was associated with prolonged LOS.[17]

Several EV strains are responsible for LRTI with different clinical severity.[18] Although EV is self-limiting and associated with less severe respiratory illness,[18] one of the strain, EV-D68 was reported to cause asthma exacerbation and severe respiratory illness.[19, 20] In this current study, there were about 10% of children infected with EV virus, and of the positive EV specimens successfully sequenced, there were three EV-71 specimens and one EV-D68 detected and one coxsackievirus B5.[16] However, they did not seem to have much difference in terms of disease burden compared to those without EV virus, may be due to its relatively smaller number of children with EV.

We detected viral co-infection in 17% of the specimens collected from children in our study, of which, PIV 1 as well as AdV, EV and RSV B were the most common viruses with such co-infection. Our study found that children with co-infections were more likely to be intubated compared to those with a single infection. However, the clinical severity of disease among children with co-infection was still controversial with some findings that suggested to have increased clinical severity while some did not due to different study designs, seasonality and pathogens covered in the studies. [21, 22]

These findings, along with the seasonal distribution of the viruses, age distribution and social background, provide important information for clinicians to understand which pathogens may be causing respiratory infections among the under-five population, thus improving their clinical practice. By knowing which pathogens are associated with the infection, clinicians can both focus on symptomatic treatment and target the specific pathogen. For example, children with influenza virus infection can be treated by oseltamivir or zanamivir. These antiviral agents can reduce the duration of illness in children.[23] Currently, there are several antiviral therapies for RSV under research.[24] Detection of viral infection of LRTI can also help to reduce the misuse of antibiotics. Furthermore, understanding which pathogens are predominant and causing a more severe disease burden is important for the development of antiviral agents, vaccines and prophylaxis treatments.

This was the first of this kind of epidemiological study for LRTI from Sarawak, and it reflected a true clinical practice of children with LRTI, showing the accurate disease burden. Nevertheless, the study has a few limitations. Study subjects were collected through convenience sampling and hence may not represent the general LRTI population; we believe children with more serious conditions were recruited during the study period. The actual disease burden for the viruses in overall LRTI may be lower, which likely would have been reflected had we included children in the study with milder LRTI disease manifestation. We also did not study

the bacteriological causes of these LRTI, although during the recruitment, if the children were to have known bacteriological causes, they would not have been recruited. Because the NP were only processed in batches due to the study nature, and sometimes weeks later, the clinicians did not have the results in hands most of the time while the children were in the wards. We also could not be completely sure that molecular evidence of viruses in the NP swab were truly the cause of the LRTI morbidity. Therefore, a further study to compare the swab-negative LRTI cases with the swab-positive cases is required. Especially in young children, prolonged shedders and the issue of difficulty getting a good sample may skew the positive isolation rates either way. Other factors that might have influenced on the prevalence of viruses and / or disease burdens include flu vaccine uptake, bacterial-viral co-infection and co-morbidities such as prematurity or chronic lung / heart diseases. This information were not available to our study, although in Sarawak, the flu vaccine uptake among children population is generally very low.

CONCLUSION

This study compared metrics for disease burden for several viruses associated with LTRI in Central Sarawak. In this study, LTRI hospitalizations due to AdV infection among children under five years of age were more severe compared to LRTI hospitalizations due to other causes, although RSV was the commonest cause among all hospitalizations. Having the diagnostic capability to determine the cause of LRTI is critically important in developing effective programs to prevent and treat infections.

ACKNOWLEDGEMENT

We thank the Director-General of Health, Malaysia for his approval to publish the findings in this study. This work was conducted with support from the Duke University, the Duke Global Health Institute, Clinical Research Centre Sibu Hospital and SEGi University Sibu Clinical Campus. We thank the pediatric doctors in Sibu Hospital and Kapit Hospital for enrolling the patients and for gathering essential clinical data.

REFERENCES:

1. Societies FoIR. The Global Impact of Respiratory Disease – Second Edition. Sheffield, European Respiratory Society. 2017.
2. (IHME) IfHMaE. Findings from the Global Burden of Disease Study 2017. 2018.
3. Statistics on Causes of Death, Malaysia, 2017 [press release]. Department of Statistics Malaysia 2018.
4. Rahman MM, Wong KK, Hanafiah A, Isahak I. Influenza and Respiratory Syncytial viral infections in Malaysia: Demographic and Clinical perspective. Pak J Med Sci. 2014;30(1):161-5.
5. Nathan AM, Rani F, Lee RJ, Zaki R, Westerhout C, Sam IC, et al. Clinical Risk Factors for Life-Threatening Lower Respiratory Tract Infections in Children: A Retrospective Study in an Urban City in Malaysia. PLoS One. 2014;9(10).
6. Khor CS, Sam IC, Hooi PS, Quek KF, Chan YF. Epidemiology and seasonality of respiratory viral infections in hospitalized children in Kuala Lumpur, Malaysia: a retrospective study of 27 years. BMC Pediatr. 2012;12:32.
7. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. Pediatrics. 2011;128(6):1053-61.
8. van Houten CB, Cohen A, Engelhard D, Hays JP, Karlsson R, Moore E, et al. Antibiotic misuse in respiratory tract infections in children and adults-a prospective, multicentre study (TAILORED Treatment). Eur J Clin Microbiol Infect Dis. 2019;38(3):505-14.
9. Toh TH, Hii KC, Fieldhouse JK, Ting J, Berita A, Nguyen TT, et al. High Prevalence of Viral Infections Among Hospitalized Pneumonia Patients in Equatorial Sarawak, Malaysia. Open Forum Infect Dis. 2019 Feb 13;6(3):ofz074.
10. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014 Dec;12(12):1500-24.
11. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-58.
12. Díaz PV, Calhoun WJ, Hinton KL, Avendaño LF, Gaggero A, Simon V, et al. Differential effects of respiratory syncytial virus and adenovirus on mononuclear cell cytokine responses. Am J Respir Crit Care Med. 1999;160(4):1157-64.
13. Lu MP, Ma LY, Zheng Q, Dong LL, Chen ZM. Clinical characteristics of adenovirus associated lower respiratory tract infection in children. World J Pediatr. 2013;9(4):346-9.
14. Hong JY, Lee HJ, Piedra PA, Choi EH, Park KH, Koh YY. Lower Respiratory Tract Infections due to Adenovirus in Hospitalized Korean Children: Epidemiology, Clinical Features, and Prognosis. Clin Infect Dis. 2001;32(10):1423-9.

15. Murtagh P, Cerqueiro C, Halac A, Avila M, Kajon A. Adenovirus type 7h respiratory infections: a report of 29 cases of acute lower respiratory disease. Acta Pediatr. 1993;82(6-7):557-61.
16. Fieldhouse JK, Bailey ES, Toh TH, Hii KC, Mallinson KA, Ting J, et al. Panspecies molecular assays detect viral pathogens missed by real-time PCR/reverse-transcriptase PCR among pneumonia patients, Sarawak, Malaysia. Trop Dis Travel Med Vaccines. 2020; 6:13.
17. Li L, Woo YY, de Bruyne JA, Nathan AM, Kee SY, Chan YF, et al. Epidemiology, clinical presentation and respiratory sequelae of adenovirus pneumonia in children in Kuala Lumpur, Malaysia. PLoS One. 2018;13(10).
18. Jacques J, Moret H, Minette D, Lévêque N, Jovenin N, Deslée G, et al. Epidemiological, molecular, and clinical features of enterovirus respiratory infections in French children between 1999 and 2005. J Clin Microbiol. 2008;46(1):206-13.
19. Moyer K, Wang H, Salamon D, Leber A, Mejias A. Enterovirus D68 in Hospitalized Children: Sequence Variation, Viral Loads and Clinical Outcomes. PLoS One 2016;11(11).
20. Biggs HM, McNeal M, Nix WA, Kercsmar C, Curns AT, Connelly B, et al. Enterovirus D68 Infection Among Children With Medically Attended Acute Respiratory Illness, Cincinnati, Ohio, July-October 2014. Clin Infect Dis. 2017;65(2):315-23.
21. Lim FJ, de Klerk N, Blyth CC, Fathima P, Moore HC. Systematic review and meta-analysis of respiratory viral coinfections in children. Respirology. 2016;21(4):648-55.
22. Goka EA, Vallely PJ, Mutton KJ, Klapper PE. Single and multiple respiratory virus infections and severity of respiratory disease: a systematic review. Pediatr Respir Rev. 2014;15(4).
23. Shun-Shin M, Thompson M, Heneghan C, Perera R, Hamden A, Mant D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. BMJ. 2009; 339.
24. Xing Y, Proesmans M. New therapies for acute RSV infections: where are we? Eur J Pediatr. 2019;178(2):131-8.