ORIGINAL ARTICLE

EPIDEMIOLOGY OF RESPIRATORY PATHOGENS IN CHILDREN WITH ACUTE RESPIRATORY TRACT INFECTION IN UKRAINE DURING 2018-2020 YEARS

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ABSTRACT

The aim: Is to provide data on the presence of potential pathogens of ARTIs in children in Ukraine.

Materials and methods: The etiology of ARTIs was investigated in 487 children in MC 'Eurolab', Kyiv, Ukraine during 2018-2020 years. Seven respiratory viruses - Respiratory Syncytial virus (*RSV*), Parainfluenza virus (*PIV*), Adenovirus (*AdV*), human Metapneumovirus (*MPV*), Rhinovirus (*RV*), human Bocavirus (*BoV*), Coronavirus (*CoV*), were identified by PCR. Qualitative detection of Influenza type A, type B, Group A Streptococcal was performed by chromatographic immunoassay. Pathogens profiles, clinical characteristics and seasonality were analyzed.

Results: 487 nasal and throat swabs from children with ARVI were collected. 400 (82,1%) samples were found to be positive: 319 swabs were positive at least for one respiratory virus, 43 children had positive rapid influenza test, 38 – positive strep test. A total of 403 viruses were identified. *RV* (27,1%), *ADV* (13,4%), *RSV* (*13,2* %), *IVA* (10,7 %) were the most commonly identified viruses.

Conclusions: Detection of viral seasonality in Ukraine and estimating of clinical features in case of infection allows predicting probable clinical course of disease, to provide, optimize the therapy and to develop preventive measures, vaccination, in particular.

KEY WORDS: acute respiratory tract infections, epidemiology, clinical characteristics, pediatrics, Ukraine

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INTRODUCTION

Acute respiratory tract infections (ARTI) are the leading cause of illness and hospitalization of children in Ukraine. ARTIs can be caused by bacteria, but they are most commonly caused by viral infections [1].

Doctor's clinical decision is usually based on interpretation of complains and clinical symptoms. The ability to distinguish viral and bacterial diagnosis is extremely important because of therapeutic consequences. It can allow the clinicians to reduce assignment of additional examination, optimize therapy and predict the course of the disease [1, 2, 3].

Prevalence of most common viruses - Respiratory Syncytial virus (*RSV*), Parainfluenza virus (*PIV*), Adenovirus (*AdV*), human Metapneumovirus (*hMPV*), Rhinovirus (*RV*), human Bocavirus (*hBoV*), Coronavirus (*CoV*) and Influenza virus (*IV*) were studied all over the world [2, 4, 5, 6, 7, 8].

Estimating etiology diagnosis in children with acute lower respiratory infection (ALRIs) - pneumonia and bronchiolitis, which are major cause of hospital admissions among children worldwide, is also very important. Severe ALRIs result in millions death in young children, 99% of these deaths are in developing countries [9].

Evidence of a viral cause of pneumonia was obtained in 62-67 % of children [6, 10, 11]. At least 26 viruses have now been associated with pneumonia. Among them – *RSV, RV, IV* A, B, and C, *MPV*, *PIV* 1, 2, 3, and 4, *BOV, COV* types 229E, OC43, NL63, HKU1, SARS, *ADV* and others [11]. The role of *RSV*, *IV*, *PIV* and *MPV* as important causes of ALRI in young children was demonstrated with statistically significant evidence in previous studies [5].

Provided studies indicate, that bacterial infections occur less frequently in children with concurrent *IVA* and *RSV* infection [12, 13]. Also the importance of viral diagnosis underlines that fact, that in case of *RSV* infection no differences were found in the temperature and white blood cell count in blood samples of patients less 3 months of age with and without positive bacterial cultures [13].

Nonetheless, results of provided research from other countries cannot be extrapolated to the entire European region. Many factors may result in variable prevalence of viruses [14]. Except viral characteristics, geographic environment, local climate during year, population structure, ethnic characteristics, and even social interaction can influence on that [15].

Thus, the importance of epidemiological studies for estimation the regional and national burden of disease due to

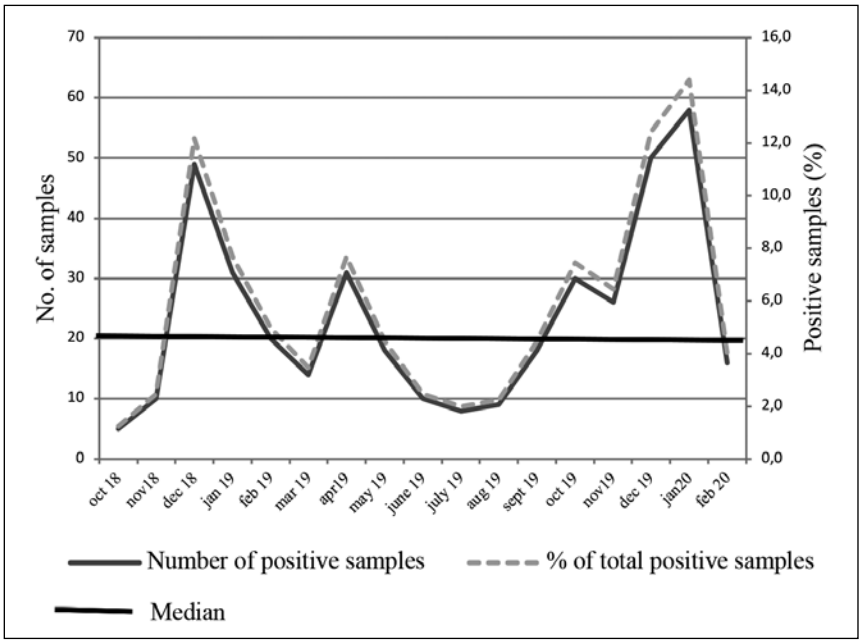

Fig. 1. Monthly infection rates of human respiratory viruses from October 18 until March 2020

these viruses has become increasingly apparent to update prevention and control strategies. Data on the epidemiology profiles of ARTIs, unfortunately, are scarce in Ukraine.

THE AIM

The objective of this study was to estimate the epidemiology characteristics and the clinical features of ARVI, caused by common respiratory pathogens in children in Kyiv, Ukraine.

MATERIALS AND METHODS

A total 487 nasal and throat swabs from children with ARVI were collected. All analyses were performed in MC 'Eurolab', Kyiv, Ukraine.

For respiratory virus analyses nasal swabs were used. Viral RNA and DNA were extracted by Ribo-prep Nucleic Acid Extraction Kit (Amplisens, Russian Federation) according to the manufacturer's instructions. cDNA were synthesized with Reverta-L RT reagents kit (Amplisens, Russian Federation). Primers Amplisens ARVI-screen – FRT PCR kit were prodused by Amplisens, Russian Federation. PCR RT were performed using Rotor Gene Q (Qiagen, Germany).

Chromatographic immunoassay for the qualitative detection of Influenza type A and type B from nasal swabs and Group A Streptococcal from throat swabs were used (CerTest Influenza A+B Spain and Cito test Strep A, Biotec, Spain respectively). Clinical Sensitivity and Specificity of tests according to the manufacturer's instructions was > 99%.

Ethics: Written informed consents were obtained from the parents or the caregiver before collecting samples.

RESULTS

487 nasal and throat swabs from children with ARVI were collected during the period from October 2018 until March 2020. Overall, 400 (82,1%) out of 487 samples were found to be positive: 319 swabs were positive at least for one respiratory virus, 43 children were positive for rapid influenza test, 38 – were positive for strep test. A total of 403 viruses were identified. Among 400 enrolled children 231 were boys (57,8 %) and 169 were girls (42,2 %). Median age was 6 years, range 2 month - 16 years. 236 (59,0 %) virus-positive samples were collected from outpatients and 164 (41,0 %) from inpatients.

Single infections predominated over mixed infections. Among positive samples 2 virus were identified in 43 cases (10,8%), more than 2 virus – in 1 case (0,25%).

Among respiratory viruses *RV* (27,1%) and *ADV* (13,4%) prevailed; *RSV* (13,2 %), *IVA* (10,7 %) and *COV NL-63, 229E* (8,9%) showed a higher frequency than *MPV* (8,4%), *PIV* (7,9 %), *BOV* (7,4 %) and *COV HKU-1, OC43* (3,0%).

SEASONAL DISTRIBUTION

The infection rate exceeded the median from November 2018 to January 2019, from April 2019 to May 2019 and from November 2019 to January 2020. Major peaks occurred in November 2018 and January 2020 (Fig.1).

RV (Fig. 2A) circulated during all seasons and was systematically detected. Infection rate exceeded median from September 2019 till February 2020, and was higher than during previous season.

ADV (Fig. 2B) had a higher prevalence in December 2019 – January 2020, the rate of *ADV* detection was markedly higher than during previous year throughout last winter.

RSV (Fig. 2C) showed highest prevalence in spring 2019, especially in March – April. In August – September 2019 RSV was not detected.

IVA (Fig. 2D) had two peaks during period of observation: first – from November 2018 till March 2019, second one started later, in December 2019.

COV NL-63, 229E (Fig. 2E) showed a notable peak

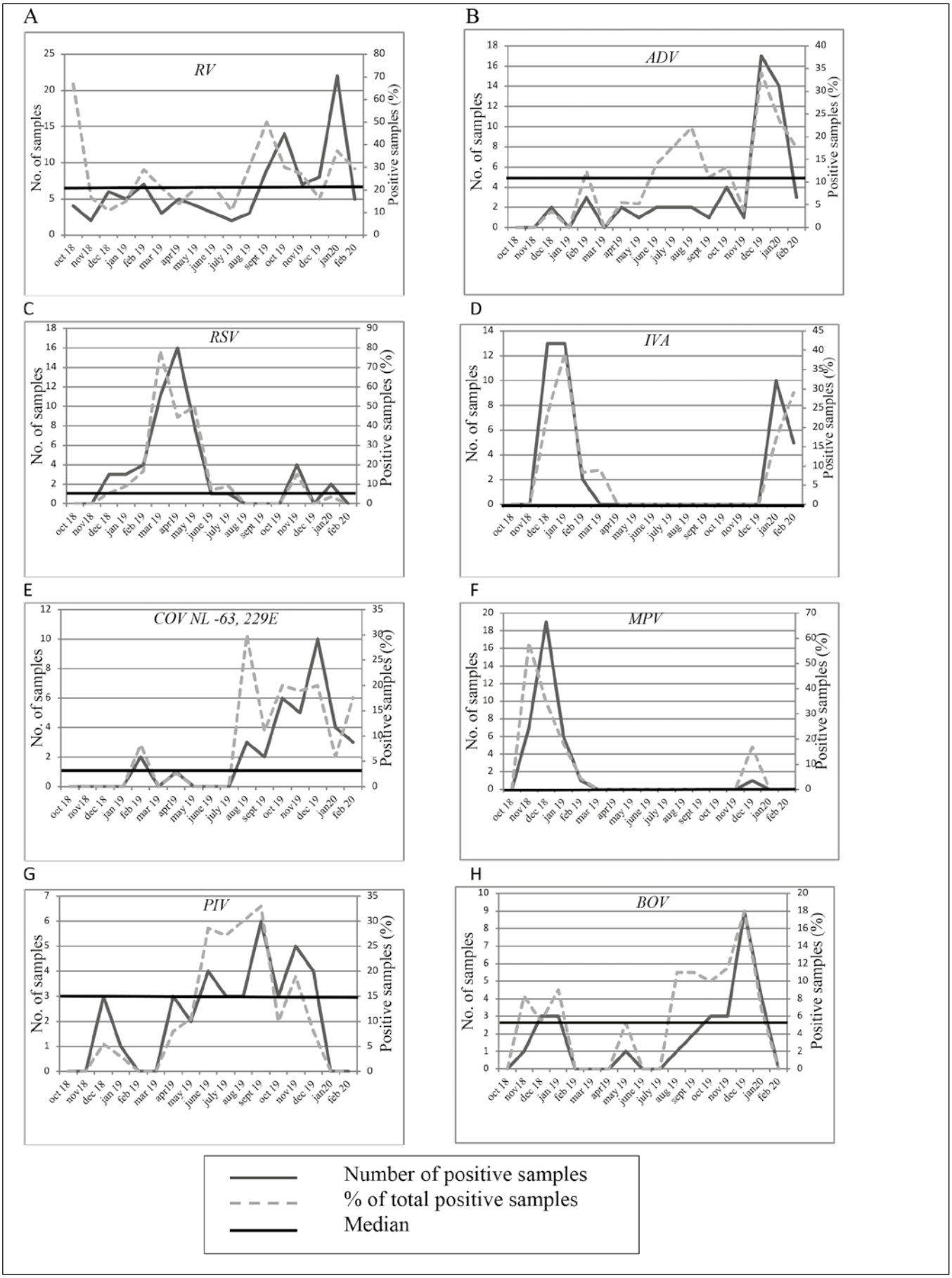

Fig. 2. Monthly infection rates of human respiratory viruses: (A) RV; (B) ADV; (C) RSV; (D) IVA; (E) COV NL -63, 229E; (F) MPV; (G) PIV; (H)BOV.

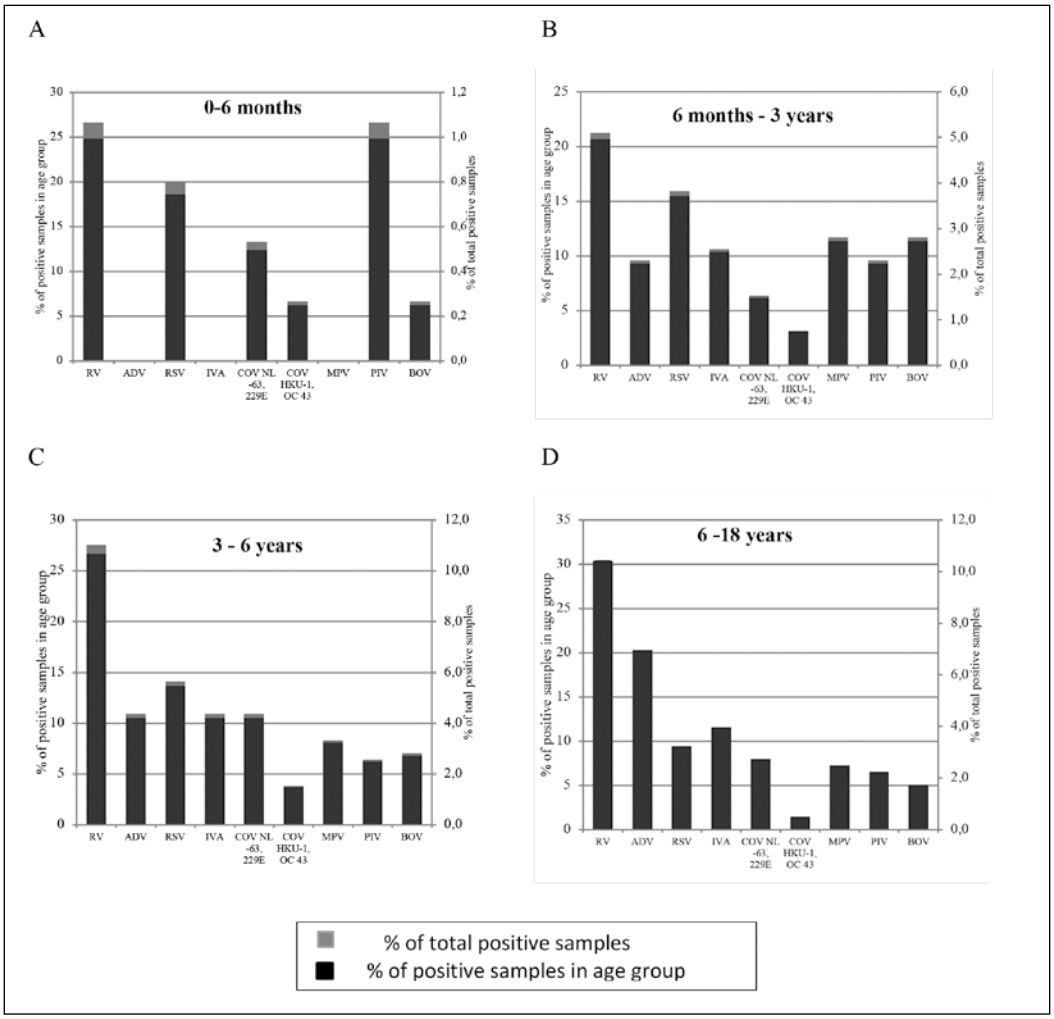

Fig. 3. Age distribution of human respiratory viruses: (A) 0-6 months; (B) 6 months – 3 years; (C) 3-6 years; (D) 6-18 years.

from august 2019 till February 2020. The most numbers of positive samples of *COV* NL-63, 229E were detected in December 2019.

MPV (Fig. 2F) was detectable only from November till early spring. In 2018 the detection rate was markedly higher, than in 2019.

The *PIV* (Fig. 2G) prevalence exceeded the median in June 2019, September 2019 and November 2019.

BOV (Fig. 2H) was detected in all seasons, the major peak was in December 2019 and the number of detected samples was higher than in winter 2018.

AGE DISTRIBUTION

For the child with ARTIs, the mean and median age were 5,8 and 5 respectively.

We compared positive detection rates of viruses in four age groups: 0-6 months (Fig. 3A), 6 months – 3 years (Fig. 3B), 3-6 years (Fig. 3C) and 6-18 years (Fig. 3D). In all age groups the most prevalent virus was *RV*. Its detection rate was 26,7% in children younger than 6 months, 21,3% in children aged 6 months – 3 years, 27,6% in children aged 3-6 years and 30,4% in children aged 6-18 years.

PIV (26,7%) and RSV (20%) were detected more often in the youngest group. In children aged 6 months – 3 years, most prevalent viruses were RSV (16%), MPV (11,7%) and *BOV*(11,7%). In children aged 3-6 years - *RSV* (14,1%), ADV (10,9%), *COV* NL -63, 229E (10,9%) and IVA (10,9%). In oldest group, *ADV* (20,3%) and *IVA* (11,6%) were detected more often than others.

CLINICAL FEATURES

To analyze the clinical characteristics of patients, we divided 319 patients with mono-infection into 2 groups – with upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI) (Tab.I). URTI included acute rhinitis, pharyngitis, tonsillitis, laryngitis, otitis media, acute sinusitis and croup. LRTI included acute bronchiolitis, bronchitis, obstructive bronchitis and pneumonia.

183 (57,4 %) patients had a clinical picture of URTI. Among them *RV* was detected in 54 (29,5 %) children (OR 1,690, CI 0,997-2,864), *COVNL-63, 229E* and *HKU-1 OC43*, - in 36 (19,6 %) children, *ADV* – in 23 (12,5 %) patients. Diagnosis of croup was established in 16 cases, and *PIV* was detected in 8 cases (50,0 %).

Table I. Etiologic Agents and Related Clinical Diagnosis. Etiologically confirmed number of cases (% of the total)

	RV	*ADV*	*RSV*	*IVA*	*COV*	*MPV*	*PIV*	*BOV*	Total
URTI	54 (29,5%)	23 (12,6%)	15 (8,2%)	17 (9,3%)	36 (19,7%)	4 (2,1%)	14 (7,7%)	20 (10,9%)	183
LRTI	27 (19,9%)	15 (11,0%)	32 (23,5%)	23 (16,9%)	4 (2,9%)	27 (19,9%)	7 (5,1%)	1 (0,7)	136
Croup	3 (18,7%)	1 (6,3%)	1 (6,3%)	0 (0,0%)	3 (18,7%)	0 (0,0%)	8 (50,0%)	0 (0,0%)	16
Wheezing	4 (13,3%)	1 (3,3%)	13 (43,3%)	2 (6,7%)	3 (10,0%)	5 (16,7%)	2 (6,7%)	0 (0,0%)	30
Pneumonia	5 (11,9%)	13 (31,0%)	5 (11,9%)	8 (19,0%)	0 (0,0%)	6 (14,3%)	5 (11,9%)	0 (0,0%)	42
Bronchiolitis	5 (29,4%)	0 (0,0%)	9 (52,9%)	0 (0,0%)	0 (0,0%)	3 (17,7%)	0 (0,0%)	0 (0,0%)	17

Table II. Mono and Co-detection with respiratory viruses. Etiologically confirmed number of cases (% of the total)

	URTIs		LRTIs	
	Mono-infection	Co-infection	Mono-infection	Co-infection
RV	54 (12,9%)	21 (5,7%)	27 (6,7%)	7 (1,7%)
ADV	23 (5,7%)	10 (2,5 %)	15 (3,7%)	6 (1,5%)
RSV	15 (3,7%)	0 (0,0%)	32(7,9%)	5 (1,2%)
IVA	17 (4,2%)	2 (0,5%)	23 (5,7%)	1 (0,2%)
COV NL -63, 229E	28 (6,9%)	6 (1,5%)	3 (0,7%)	1 (0,2%)
COV HKU-1, OC43	8 (2,0%)	1 (0,2%)	1 (0,2%)	2 (0,5%)
MPV	4 (1,0%)	1 (0,2%)	27 (6,7%)	1 (0,2%)
PIV	14 (3,5%)	6 (1,5%)	7 (1,7%)	5 (1,2%)
BOV	20 (5,0%)	5 (1,2%)	1 (0,2%)	4 (1,0%)

Table III. Combination of viral co-detection

URTIs			LRTIs	Clinical Diagnosis
RV+ADV	8	*RV+ADV*	3	wheezing, bronchitis
RV+COV NL -63, 229E	3	*RV+RSV*	2	Wheezing
RV+ IVA	2	*BOV+PIV*	2	bronchitis, pneumonia
RV+PIV	2	*RSV+PIV*	2	Wheezing
RV+BOV	2	*ADV+ IVA*	1	Pneumonia
BOV+PIV	2	*RV+COV HKU-1, OC43*	1	Wheezing
RV+COV HKU-1, OC43	1	*RV+PIV*	1	Pneumonia
BOV+ADV	1	*BOV+MPV*	1	Wheezing
ADV+COV NL -63, 229E	1	*BOV+ADV*	1	Wheezing
PIV+COV NL -63, 229E	1	*RSV+MPV*	1	Wheezing
PIV+RV+COV NL -63, 229E	1	*COV NL -63, 229E + ADV*	1	Bronchitis
		COV HKU-1, OC43 + PIV	1	Wheezing

LRTI were diagnosed in 136 (42,6 %) patients. In patients with infection, caused *MPV*, LRTI was diagnosed in 87% cases (27 from 31). *MPV* was responsible for pneumonia, obstructive bronchitis, bronchiolitis and bronchitis and was significantly more frequent cause of LRTI (OR 11,085, CI 3,777-32,535). High proportion was also admitted in children with *RSV* - LRTI was diagnosed in 67,9 % cases, *RSV* also was significantly more frequent cause of LRTI (32 from 47) (OR 5,062, CI 2,694-9,509). *RSV* was detected commonly in children with wheezing (OR 7,750, CI 2,669-22,506), among them 52,9% had bronchiolitis and 43,3% cases had obstructive bronchitis.

Diagnosis of pneumonia was confirmed in 42 (13,1 %) patients. Pneumonia was caused by *ADV* in 13 cases

(30,9 %), in 8 cases (19 %) – *IVA*, in 6 cases (14,3%) – *MPV*. *ADV* was significantly more frequent identifiable viral infection in pneumonia cases (OR 3,642, CI 1,752-7,573)

CODETECTION OF RESPIRATORY VIRUSES

Generally, codetection was found in 43 children (Tab. II). 26 children (60,5%) had URTIs and 17 patients (39,5%) had LRTIs. The most common virus was RV – it was detected in 28 children. Among them in 21 patients had URTIs and in 7 children had LRTIs. ADV, detected in 16 cases, in combination cased URTIs in 10 children and LRTIs in 6 children with codetection.

11 codetection combinations were estimated in URTIs and 12 combinations in LRTIs (Tab. III). The most common combination was *RV+ADV,* detected in 11 children, 8 of them had URTIs and 2 had bronchitis and 1 - wheezing. Among 17 children with co-infection and clinical sings of LRTIs, 11 children (64,7%) were in age group 3 – 6 years.

DISCUSSION

This study was carried out in Kyiv, Ukraine from October 2018 till March 2020. The aim of this study was to investigate the seasonality and the role of respiratory pathogens in ARTIs among 487 children.

RV (27,1 %) and *ADV* (13,4 %) were the most commonly identified viruses, followed by *RSV* (13,2 %), *IVA* (10,7 %), *COV* NL-63, 229E (8,9%) and *MPV* (8,4%). Other viruses such as *PIV*, *BOV* and *COV* HKU-1, OC43 were identified in small proportions (7,9 %, 7,4 % and 3,0 % respectively).

Single infections predominated over mixed infections (79,5 % vs. 20,5%), which was consistent with previous observation [7, 8, 16].

The epidemic season of respiratory viruses ranged from 3 to 4 Month (exceed median), with peaks in November (2018) and January (2020). This data demonstrate the high prevalence of infection rate in winter months, consistent with previous studies [17].

In this study definite seasonality was shown by *RSV*, *MPV* and *IVA*. *RSV* raised in prevalence in early spring, when *IVA* and *MPV* had winter seasonality. During observation, it was founded, that the etiological spectrum of ARVI during last two years was changed. These results differ from previous reports and can be explained by climatic features – mean temperature, humidity, wind speed etc. [15, 18, 19].

RV, *PIV* and *BOV* circulated persistently throughout the study with periodic elevation of infection rate. Generally, these results were consistent with previous reports [15, 17]. Further observation is needed for estimation epidemiological patterns of these viruses.

We observed increase of infections rate of *ADV* from December 2019 and *COV* NL-63, 229E from August 2019 in our study.

RV was the most prevalent virus in all age group of children in our study, and it matches the other results [7, 8, 17]. In children aged less than 6 month *PIV* and *RSV* were detected more often than others. The detection rate of *RSV* decreased with increasing of age, while proportion of *ADV* and *IVA* increased with age. Age distribution of *RSV* and *IV* are similar to data observed in previous study [15, 20].

Children with URTI consist 57,4 % of all enrolled patients. Most common were *RV* (29,5 %), *COV* NL-63, 229E and HKU-1, OC43 (19,6 %) and *ADV* (12,5%). High prevalence of *RV* in children with ARVI already was showed in previous study [4]. 50% cases of croup, associated with respiratory insufficiency, were caused by *PIV*.

Most common viruses detected in LRTIs were *RSV* (OR 5,062, CI 2,694-9,509), *MPV* (OR 11,085, CI 3,777-32,535) and *RV*. In addition, among children with *RSV* and *MPV*, proportion LRTIs was bigger than URTIs. High prevalence of *RSV* and *RV* were previously showed in others publications [18, 20]. In our study *RSV* caused the 52,9% cases of bronchiolitis, 43,3% of wheezing. As reported earlier, *RSV* was the first most common pathogen in LRTIs [15]. Interestingly, that previous study showed that two or three viruses have been detected in 10–20% of children with pneumonia [11]. In our study this rate was 6,7 %.

MPV, *RSV* and *PIV* are known as common causative pathogens of pneumonia in children [5]. Etiologic structure of viral pneumonia in our study was: *ADV* (30,9%), *IVA* (19%), *MPV* (14,3%). *ADV* was significantly more frequently identifiable viral infection in pneumonia cases (OR 3,642, CI 1,752-7.573). In study, conducted Lin MR et al, *ADV* types 3 and 7 infections were associated with the risk of LRTIs – pneumonia and respiratory distress requiring both oxygen supplementation and intensive care. Among the 63 pneumonia cases, most (65%) involved a single lobe and 11 (17 %) exhibited pleural effusion [21]. 21% of the *ADV* single infections were diagnosed with pneumonia in other study [22]. Similar infection rates of *IVA* among children with pneumonia were showed in study [11].

HRV (65,1 %) and *ADV* (37,2%) were mainly involved in mixed infections, as would be expected from their overlapping seasonal distribution, and was seen in previous studies [19, 22]. Mixed infection were detected in children with ARTIs more often, than in patients with LRTIs (60,5 % and 39,5 %, respectively). The most common combination of co-infection was *RV+ADV* (25,5 %). In study, conducted Chen J et al. this combination was also often detected [17]. Mixed infections were not estimated in children less than 6 month. Most of co-detection cases were revealed in children aged 3-6 years. Notably, children are attending day care usually at this age.

CONCLUSIONS

Detection of viral seasonality in Ukraine and estimation of clinical features in case of infection allows to predict probable clinical course of disease provide, optimize the therapy and to develop preventive measures, vaccination, in particular. *RV* was the most prevalent virus in all age group of children in our study, and it matches the other results.

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