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Etiological spectrum of pneumonia in children in Kyiv, Ukraine

Abstract. *Background.* In Ukraine over the past 20 years, the incidence of pneumonia in children has increased. The aim of the study is to assess the contribution of respiratory viruses and bacteria to pneumonia in children in Ukraine. **Materials and methods.** The etiology of community-acquired pneumonia was studied in 175 children at Medical Center "Eurolab" and Clinical Hospital 2 (Kyiv, Ukraine) over 2018–2022. Viral and bacterial pathogens were detected using polymerase chain reaction, chromatographic immunoassay. **Results.** The prevalence of viral pneumonia among total cases of pneumonia was 78.9 % in Kyiv during 2018–2022. Thirty-seven (21.1 %) cases of CAP were classified as bacterial. The most common were respiratory syncytial virus (18.1 %), metapneumovirus (13 %), adenovirus (10.1 %), parainfluenza virus (10.1 %). The other causative viral agents were influenza virus type A (7.2 %), rhinovirus (5 %), bocavirus (2.9 %), SARS-CoV-2 (1.4 %) and measles virus (1.4 %). Etiological spectrum is similar to the results of studies conducted in other European countries. **Conclusions.** Respiratory viruses, particularly respiratory syncytial virus and metapneumovirus, are the major contributors to community-acquired pneumonia in children in Kyiv.

Keywords: pneumonia; children; respiratory infection; viral infection

Introduction

Pneumonia remains the leading cause of morbidity in children worldwide and accounts for 14 % of all deaths in patients under 5 years of age. In 2019, pneumonia caused the death of 740,180 children [1]. Over the past decades, there have been significant changes in the epidemiology, etiology, and clinical picture of community-acquired pneumonia (CAP) in children. The widespread implementation of vaccination against *Streptococcus pneumoniae* (*S.pneumoniae*) and *Haemophilus influenzae* type B (HiB) has reduced the incidence of total and bacterial CAP [2].

Both the effectiveness of vaccination and an increase in the ability to detect the virus by molecular diagnostic methods have updated the understanding of CAP etiology in children. The latest studies on the etiology of pneumonia show that the proportional contribution of respiratory viral infections as causative agents of CAP has increased [2–4]. Among them the most significant are respiratory syncytial virus (RSV), influenza virus (IV), parainfluenza virus (PIV), rhinovirus (RV) and adenovirus (AdV).

Detection of CAP etiology can modify the clinical decision in children with pneumonia. First of all, antimicrobial therapy is not required for children with viral pneumonia [5, 6]. Antiviral treatment can be provided in children with CAP caused by influenza virus [5, 7]. In case of bacterial CAP, rational prescribing of antibiotics is highly important and depends on the etiology, age, local vaccination policies and resistance patterns [8].

In Ukraine, the incidence of pneumonia in children has unfortunately increased over the past 20 years [9]. The pneumococcal conjugate vaccine (PCV) is not included in the national immunization program, and vaccination coverage in the country is low. HiB vaccination is the funded program for national immunization from 2006. In the following years, HiB vaccination coverage increased and reached 87.2 % in 2021 [10]. Therefore, the study of the etiological spectrum of CAP in Ukrainian children and comparison with data from the European region are necessary for the development of effective prevention and optimization of treatment.

The purpose of this study was to assess the contribution of respiratory viruses and bacteria to pneumonia in children of Ukraine.

Materials and methods

During study period (2018–2022), in total 175 cases of CAP in children were analyzed. All of them were examined and received treatment in the Medical Center “Eurolab” and Children’s Clinical Hospital 2 in Kyiv, Ukraine.

CAP was diagnosed in the presence of a typical clinical picture: cough, tachypnea, hypoxemia, decreased breath sounds, crackles or rales on auscultation of lung fields. One hundred and seventeen (66.9 %) cases of pneumonia were confirmed by chest X-ray (CXR) (presence of any alveolar or interstitial opacity), in 19 (10.9 %) cases, characteristic changes were detected during ultrasound examination.

The nasopharyngeal swabs were collected from participants by a trained nurse. A total of 8 viruses (RSV, PIV type 1–3, metapneumovirus (MPV), AdV, RV, coronaviruses OC43, 229E, HKU1 and NL63, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) and 2 bacteria — *Mycoplasma pneumoniae* (*M.pneumoniae*) and *Chlamydomphila pneumoniae* (*C.pneumoniae*)) were detected using polymerase chain reaction (PCR).

The detection of pathogens involved extraction of DNA/RNA from samples using RIBO-prep nuclear acid extraction kit (AmpliSens, Russian Federation); reverse transcription (RT) and multiplex PCR with REVERTA-L RT reagents kit and primers AmpliSens ARVI-screen — FRT PCR kit and AmpliSens Mycoplasma pneumoniae/Chlamydomphila pneumoniae-FRT PCR kit (AmpliSens, Russian Federation). For SARS-CoV-2 testing, the reagents DNA/RNA-Mag (XEMA, Ukraine) were used. Rotor-Gene Q (Qiagen, Germany) was applied for RT-PCR. All procedures were performed according to the manufacturer’s instructions.

Chromatographic immunoassay was used for qualitative detection of influenza type A and type B in nasal swabs (CerTest Influenza A + B, Spain). Determination of measles IgM and IgG was carried out using the Measles virus IgM micro-capture ELISA and Measles virus IgG ELISA (IBL International GmbH, Hamburg, Germany). The ELISA kit EQUI Mycoplasma pneumoniae IgG (Ekvitestlab, Ukraine) was used for detection of IgG to *M.pneumoniae*, the EQUI Chlamydomphila pneumoniae IgG kit (Ekvitestlab, Ukraine) — for detection of IgG to *C.pneumoniae*. In all cases, whole blood was collected for complete blood count and C-reactive protein (CRP) tests.

All cases of CAP were divided into two groups based on probable pneumonia etiology:

— bacterial cases (lobar pneumonia with empyema, bacterial pathogen detected by PCR or confirmation of bacterial etiology by seroconversion, significant changes in complete blood count — increased number of neutrophils, leukocytes, high level of CRP);

— viral pneumonia (detection of at least one respiratory virus, unchanged complete blood count, CRP, interstitial pneumonia, peribronchial cuffing, focal bilateral involvement).

Odds ratios were used to analyze cases of hospitalization depending on the etiology of pneumonia and the age of the

child. A p-value < 0.05 was considered statistically significant.

Ethics. This study was performed in accordance with the Declaration of Helsinki. Written informed consents were obtained from the parents or the caregivers of the patients before collecting samples.

Results

The diagnosis of CAP was confirmed in 175 children from October 2018 to February 2022. The male (n = 99) to female (n = 76) ratio was 1.3 : 1, the mean and median age were 4.8 and 4 years, respectively (age range was 5 months to 18 years). 19.4 % of patients were under 2 years of age, 39.4 % aged 2–5 years and 41.1 % were older than 5 years. The percentage of children, who had received PCV, was 52.5 %. Only 33.1 % of patients received flu vaccine annually.

The total amount of viral pneumonia was 138 (78.9 %) cases, bacterial pneumonia — 37 (21.1 %) cases.

The peak incidence of CAP usually occurs during the cold season in continental climate. In 2018/2019 season, 49 (28 %) children were diagnosed with CAP. Among them, 35 (71.4 %) had viral pneumonia. During the next season (2019/2020), 48 (27.4 %) children were diagnosed with CAP, 36 (75 %) of them had pneumonia of viral etiology.

During restriction measures implemented to prevent SARS-CoV-2 infection spreading, we observed a decreased amount of pneumonia cases in children. In 2020/21 season, only 15 (8.6 %) cases of pneumonia were confirmed, of which viral etiology was found in 14 (93.4 %) cases. Analysis of 2021/22 season showed that 36 (20.5 %) children were diagnosed with CAP, of which 31 (86.1 %) had viral pneumonia (Fig. 1).

During the spring-summer periods, the incidence of pneumonia in children was traditionally lower. In 2019, the total number of pneumonia cases was 13 (7.4 %), in 2021 — 14 (8 %). The percentage of viral pneumonia among them was 84.6 and 78.6 %, respectively. During March and April 2020, patients were not admitted to the Eurolab Medical Center, and the prevalence of pneumonia was not studied.

Etiological spectrum of viral pneumonia

In 96 (69.5 %) of 138 cases, the causative agent of viral pneumonia was detected. In our study, RSV was most often detected in children with CAP (25/138). The other causative viral agents were MPV (18/138), AdV (14/138) and PIV

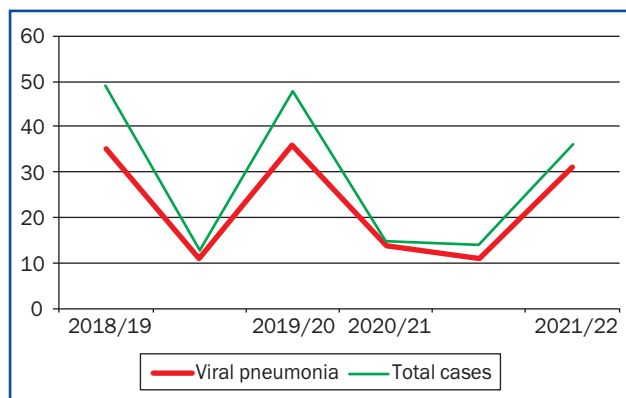


Figure 1. Total number of pneumonia cases and number of viral pneumonia cases during 2018–2022

(14/138). Less frequently, we detected IVA (10/138), RV (7/138), bocavirus (BoV) (4/138), SARS-CoV-2 (2/138). In 2018, pneumonia in 2 children was caused by the measles virus (2/138) (Fig. 2).

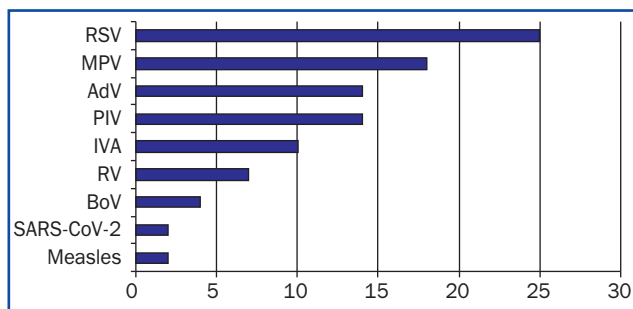


Figure 2. Etiological spectrum of viral pneumonia in children in 2018–2022

Etiological spectrum of viral pneumonia was different during the study period. In 2018/19 season, most cases of CAP were caused by MPV (7/35) and IVA (7/35). We detected RSV (3/35), AdV (2/35), RV (2/35) and measles virus (2/35) less frequent (Fig. 3a).

During the same period in 2019/20 season, we detected AdV (10/36), RV (5/36), IVA (2/36), PIV (2/36) and RSV (1/36). In one child, coinfection of RSV and PIV led to clinical presentation of pneumonia (Fig. 3b).

In 2020/21 season, MPV (9/14) and BoV (1/14) were isolated in children with viral pneumonia (Fig. 3c).

Among children with viral CAP in 2021/22 season, RSV (18/31), AdV (3/31), BoV (3/31), MPV (2/31) and IVA (1/31) were detected (Fig. 3d).

Etiological spectrum of viral pneumonia in spring-summer was also different during the study periods in 2019 and 2021.

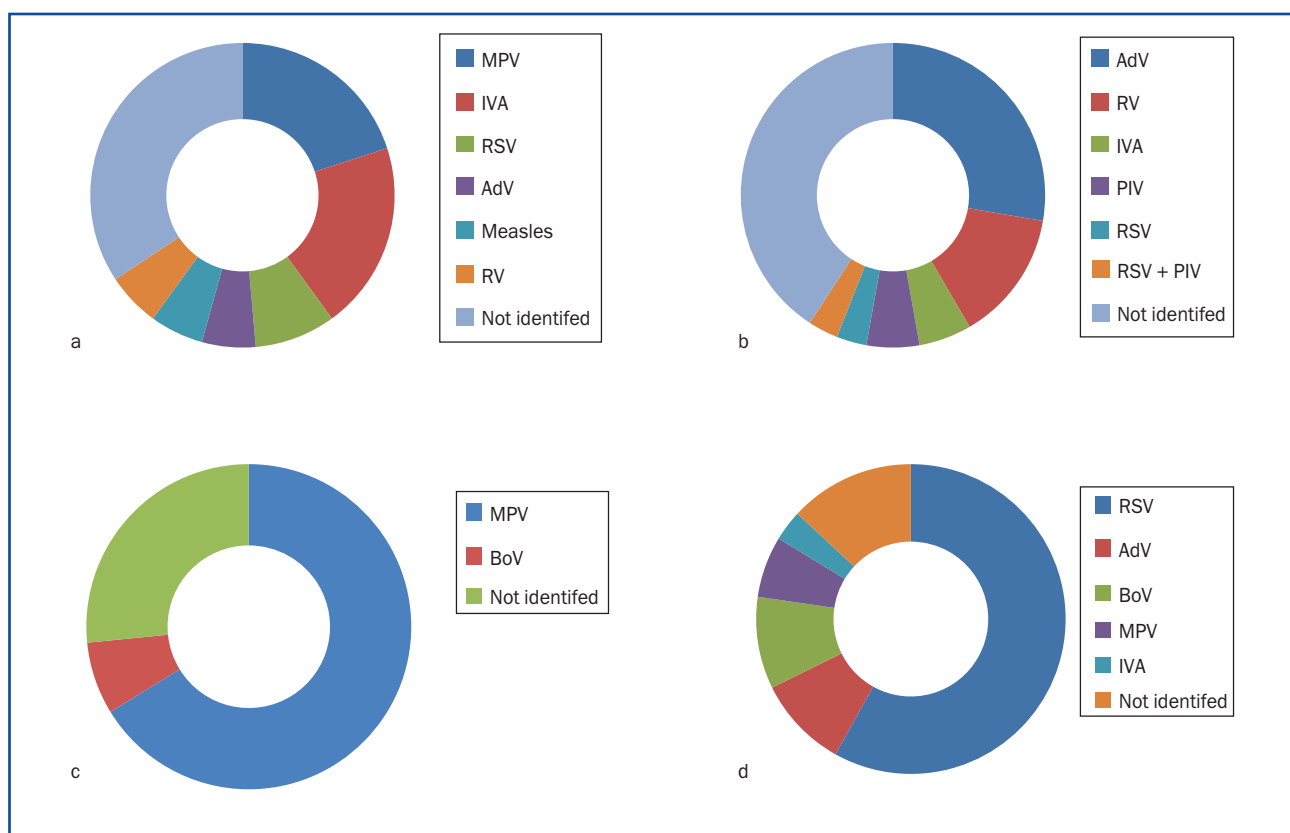


Figure 3. Etiological spectrum of viral pneumonia in seasons: a – 2018/19, b – 2019/20, c – 2020/21, d – 2021/22

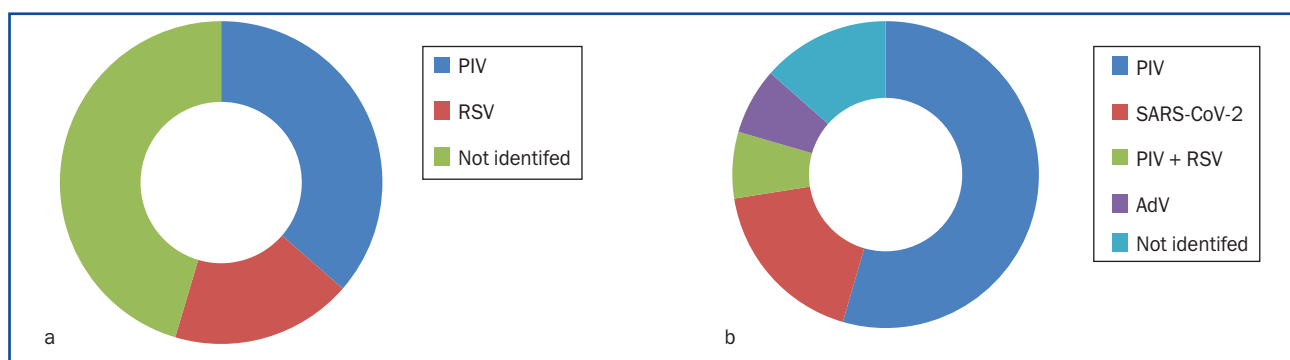


Figure 4. Etiological spectrum of viral pneumonia in spring-summer: a – 2019, b – 2021

In 2019, PIV (4/11) and RSV (2/11) caused pneumonia most frequently (Fig. 4a). In 2021, PIV (6/11), SARS-CoV-2 (2/11), AdV (1/11), coinfection of PIV and RSV (1/11) were revealed in children with CAP (Fig. 4b).

The CXR in viral pneumonia with typical changes are presented in Fig. 5, 6.

Age-related features of the clinical course of viral pneumonia

We compared the incidence of viral pneumonia in different age groups. In our study, viral pneumonia was diagnosed in 32 (23.2 %) children under 2 years of age, in 58 (42.5 %) aged 2–5 years and in 48 (34.8 %) older than 5 years.

Children under 5 years of age with viral pneumonia were hospitalized much more often than older patients. Fifty-nine (78.1 %) children under the age of 5 needed oxygen therapy, infusion therapy and medical support. Only 10 (32.1 %) children with viral pneumonia aged 5 and over were hospitalized (odds ratio 7.2323, confidence interval 3.1817 to 16.4398, $p < 0.05$) (Fig. 7).

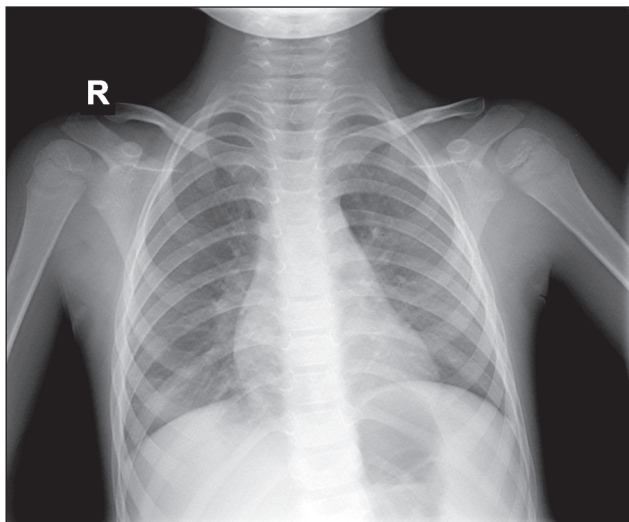


Figure 5. Viral pneumonia caused by RSV (boy, 6 years)

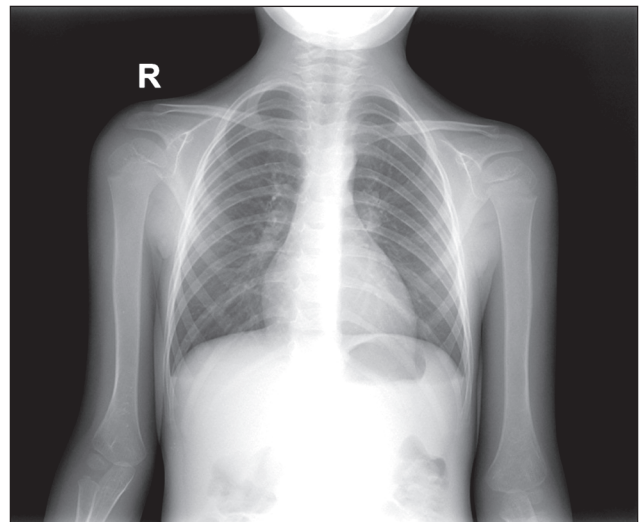


Figure 6. Viral pneumonia caused by AdV (boy, 5 years)

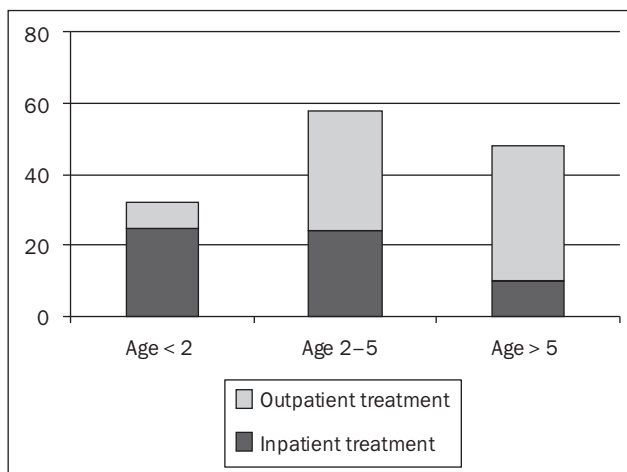


Figure 7. The incidence of hospitalization among children with viral pneumonia depending on age

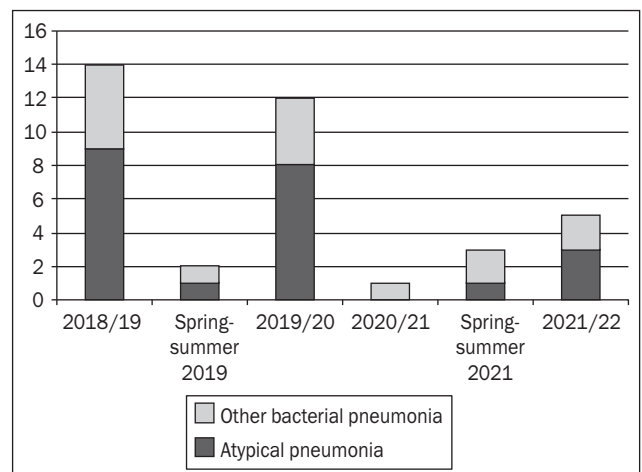


Figure 8. The incidence of atypical pneumonia among total cases of bacterial pneumonia

Etiological spectrum of bacterial pneumonia

During the study period, 37 (21.1 %) cases of CAP were classified as bacterial. Only 8 (21.6 %) of 37 children received full vaccination with PCV. *M.pneumoniae* was detected in 14 cases of CAP, *C.pneumoniae* — in 8. The percentage of pneumonia caused by *M.pneumoniae* and *C.pneumoniae* was high (60–66.7 %) during 2018/19, 2019/20 and 2021/22 seasons (Fig. 8).

The CXR in bacterial pneumonia with typical changes are presented in Fig. 9, 10.

Discussion

This study was conducted in Kyiv, Ukraine, in 2018–2022. The purpose of this study was to reveal the etiological spectrum and the role of respiratory viral pathogens in CAP in children.

In this study, the significant contribution of respiratory viruses to childhood pneumonia in Ukraine was shown. The prevalence of viral pneumonia among total cases of pneumonia in 2018–2022 was 78.9 %. These results can be compared with the frequency of detection of viruses as causes of pneumonia in children in other studies [3, 11–15].

This study demonstrated that most cases of pneumonia in children are associated with RSV (18.1 %), MPV (13 %), AdV (10.1 %) and PIV (10.1 %). Other causative viral agents are IVA (7.2 %), RV (5 %), BoV (2.9 %), SARS-CoV-2 (1.4 %), and measles virus (1.4 %). This etiological spectrum is similar to the results of studies conducted in other European countries [15, 16]. RSV continues to be the major causative viral agent of pneumonia in children globally [3, 17].

During four epidemiological seasons, the etiological spectrum of viral pneumonia in children differed. In 2018/19 season, MPV (20 %), IVA (20 %) and RSV (8.6 %) were more common. According to a recently published review, MPV caused 14.2 million cases of lower respiratory tract infections and 16,100 deaths among children under 5 years of age worldwide in 2018 [18]. Also, in 2018 the global burden of influenza-associated respiratory infections in children under 5 years was estimated. IV infection caused 7 % cases of acute respiratory diseases and 4 % of deaths from acute respiratory infections [19]. It should be noted that all children with pneumonia caused by the influenza virus in our study were unvaccinated.

During the following 2019/20 season, AdV caused CAP in 27.7 % cases, RV — in 13.9 %, IVA and PIV — in 6.5 %. The overall frequency of AdV as a cause of non-bacterial pneumonia in children in the world is lower than RSV — about 10 %. ADV types 3 and 7 can cause fatal disease in previously healthy children [20].

We observed a decreased number of total cases of CAP in children during 2020/21 season. In this period, the non-pharmacological interventions to prevent SARS-CoV-2 circulation were applied in Ukraine, as in other European countries. A decrease in the number of pneumonia cases in children is probably related to the cessation of circulation of RSV, the main causative agent, in the European region [21–23]. RSV epidemics were observed only in France and Iceland. These countries had softer restriction and kept their primary schools open. The start of RSV circulation was noticed from mid-May 2021 in other countries — Sweden, Netherlands, Spain etc. [21, 22]. In our study during

2020/21 season, 64.2 % cases of viral pneumonia were caused by MPV, 7 % — by BoV.

The last 2021/22 season showed a high percentage of RSV detection in children with viral CAP — 58.1 %, AdV — 12.9 %, BoV — 9.6 %. During the last two seasons, we observed a more frequent detection of BoV as the causative agent of CAP (7–10 %), which is consistent with previous studies [24]. In the warm seasons, we detected a higher prevalence of PIV infection (36.4 % in 2019 and 54.5 % in 2020) in children with CAP. This can be explained by the seasonal distribution of PIV type 3 [25].

We observed a significant prevalence of hospitalization of children under 5 years of age with viral pneumonia ($p < 0.05$). The present results confirm a high prevalence of viral CAP in children in Ukraine. Further investigations should be performed in Kyiv and other regions, because the results could dramatically reduce the proportion of unnecessary antimicrobial treatments for pediatric CAP in Ukraine.

In our study, only 21.1 % cases of CAP in children were classified as bacterial. A small number of bacterial pneumonia cases may reflect the effect of high PCV vaccination coverage among children in Kyiv. The percentage of bacterial pneumonia caused by *M.pneumoniae* and *C.pneumoniae* was high (60–66.7 %) during the majority of seasons in the period of study. The most frequent bacterial pathogen was *M.pneumoniae* — 8 % of total cases of CAP and 37.8 % cases of bacterial CAP. Similar results were revealed in previous studies [13, 26]. *C.pneumoniae* was detected in 4.5 % of children with CAP and in 21.6 % of children with bacterial CAP. The incidence of pneumonia caused by *C.pneumoniae* in other countries is heterogeneous and ranges from 0.5 to more than 5 % [27].

Identifying the etiology of bacterial pneumonia is extremely important for antibacterial therapy. More extensive studies are needed to clarify the incidence of bacterial pneumonia in other regions of Ukraine. The study on the etiological spectrum of pneumonia in children should be continued to develop prevention and treatment strategies. Obviously, PVC should be included in the national immunization program in the shortest possible time.

Our results do not show significant differences in the etiological spectrum of CAP in children compared to other

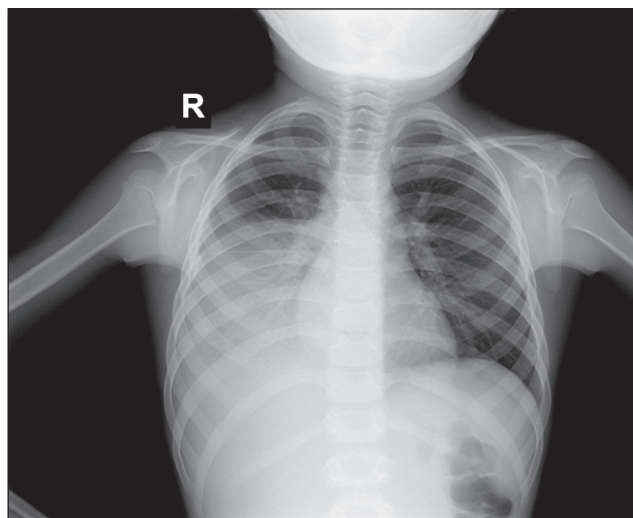


Figure 9. Bacterial right-side lobar pneumonia and empyema (boy, 9 years)

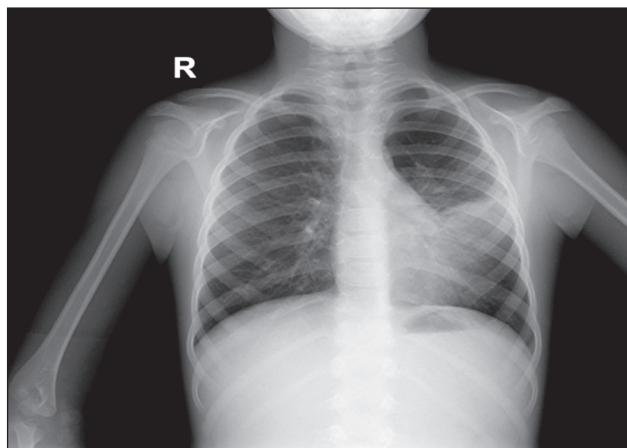


Figure 10. Bacterial pneumonia caused by *Mycoplasma pneumoniae* (boy, 7 years)

European countries. An increase in the incidence of childhood CAP in Ukraine is most likely related to the improvement of pneumonia diagnosis in Ukraine in general, on the one hand, and the deterioration of the quality of medical care in the occupied territories, on the other.

Conclusions

Much progress has been made in the prevention, diagnosis and treatment of pneumonia in children during the last three decades. This study performed in Kyiv showed the contribution of respiratory pathogens to childhood pneumonia in Ukraine. The findings highlighted the importance of RSV and MPV infection in children with CAP. Moreover, we found high prevalence of atypical pathogens in the etiology of bacterial pediatric CAP. Although further studies are needed, these results suggest that determining the etiology of CAP in children may optimize antibiotic use and improve treatment and prevention strategies.

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Етіологічний спектр пневмоній у дітей у Києві, Україна

Резюме. Актуальність. В Україні протягом останніх 20 років відмічається зростання захворюваності на пневмонію серед дітей. **Мета:** оцінити роль респіраторних вірусів і бактерій в етіології пневмоній у дітей в Україні. **Матеріали та методи.** Етіологія позалікарняних пневмоній була встановлена в 175 дітей, які отримували лікування в медичному центрі «Євролаб» і клінічній лікарні № 2 (Київ, Україна) протягом 2018–2022 рр. Для визначення вірусних та бактеріальних патогенів були використані метод полімеразної ланцюгової реакції, хроматографічний імуноаналіз. **Результати.** Серед усіх випадків пневмоній вірусна пневмонія визначалася в 78,9 %. У 37 (21,1 %) пацієнтів хвороба була класифікована

як бактеріальна. Найбільш часто виявлялися респіраторно-синцитіальний вірус (18,1 %), метапневмовірус (13 %), аденовірус (10,1 %), вірус парагрипу (10,1 %). Серед інших були виділені вірус грипу А (7,2 %), риновірус (5 %), бокавірус (2,9 %), SARS-CoV-2 (1,4 %) та вірус кору (1,4 %). Етіологічний спектр схожий з результатами досліджень, проведених в інших країнах Європи. **Висновки.** Респіраторні віруси, а саме респіраторно-синцитіальний вірус та метапневмовірус, є основними причинами позалікарняних пневмоній у дітей у Києві.

Ключові слова: пневмонія; діти; респіраторна інфекція; вірусна інфекція