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Investigation of the characteristics of patients with community-acquired infections

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1 INTRODUCTION, LITERATURE REVIEW

1.1 The public health significance of infectious diseases

Until the mid-20th century, communicable diseases were the leading cause of death and thus represented the most significant public health problem worldwide. Although the morbidity and mortality associated with infectious diseases have declined significantly in developed countries in recent decades, largely due to advances in medical science, improvements in access to healthcare and enhanced sanitation, their public health significance remains substantial. Epidemiological studies indicate that communicable diseases continue to be a significant cause of hospital admissions and associated mortality. In addition, the treatment of patients with infections represents a substantial financial burden to healthcare systems on a global scale. The public health significance of infectious diseases is further emphasised by the emergence of new pathogens as a consequence of human activity impacting upon ecosystems, thereby facilitating the outbreak of epidemics. The increasing frequency of antibiotic resistance, along with the spread of multidrug-resistant bacterial strains across communities, also poses a significant public health concern. In addition, the rapid growth in international passenger traffic has increased the risk of introducing infectious agents from one country to another, which can easily spread among susceptible populations. This is one of the main reasons why the new coronavirus disease has spread so rapidly across many countries and had a significant impact on public health systems worldwide.

1.2 Infections and colonisations detected in healthcare facilities

It is important to distinguish between healthcare-associated infections (HAIs) and community-acquired infections (CAIs) diagnosed in healthcare facilities.

1.2.1 Healthcare-associated infections

A HAI is an infection that develops 48 hours after a patient's admission to hospital, as a result of care, and was not present or incubating at the time of admission or that occurs in 30 days following the treatment. HAIs can affect the patient, the healthcare worker, as well as any other person who comes into contact with healthcare (volunteer, visitor). These infections pose a serious risk to patients and are among the most common complications associated with the delivery of healthcare services. The increasing frequency of HAIs poses a significant challenge to healthcare institutions. In addition to resulting in increased morbidity and mortality, HAIs lead to prolonged hospital stays and contribute to an increase in the economic burden on healthcare systems. According to epidemiological studies, intensive care units register the highest incidence of HAIs, the majority of which are associated with the use of invasive devices (endotracheal tubes, vascular and bladder catheters) and various procedures (surgery). However, these infections are largely preventable with appropriate infection control activities. The most commonly reported HAIs due to various multidrug-resistant bacteria include urinary tract infections, ventilator-associated pneumonias, surgical site infections and bloodstream infections. In addition, HAIs can be attributed to gastrointestinal infections caused by *Clostridioides difficile*.

1.2.2 Community-acquired infections

In addition to HAIs, there is an increased health risk from infections introduced into healthcare facilities from the area served. CAIs were defined as infections that are clinically evident at the time of hospital admission or diagnosed within 48 hours of it without any previous encounter with healthcare (pl. dialysis care, same-day surgery/oral surgical procedure, regular outpatient care). CAIs can occur in any hospital unit, but some studies have found a higher incidence of these infections among inpatients in internal medicine wards. The development of CAIs are typically attributed to a combination of factors, including inadequate housing, poor social and hygienic conditions, limited access to adequate healthcare, and exposure to asymptomatic carriers of pathogenic microorganisms. These infections can be transmitted through various routes including droplets, contaminated food or water, or through insect bites. CAIs are accompanied by symptoms specific to the disease, usually caused by obligate pathogenic agents. The severity of the course of infection can vary, ranging from mild to severe manifestations, and in certain cases, the outcome can be fatal. CAIs can cause different types of diseases depending on the location of the infectious agents in the body, which are discussed in more detail in chapter 1.3.

1.2.3 Colonisations

In addition to infections detected in healthcare settings, colonisations, where the pathogen is present on the skin, mucous membranes or other typically non-sterile tissues or body fluids (faeces, sputum) without causing clinical symptoms, are of particular importance. The occurrence of colonisations among patients treated in hospitals facilitates the spread of pathogens in healthcare setting, as they are detected late in the absence of clinical signs, often preventing the timely implementation of infection control measures to avoid contact spread.

1.3 Significance, main types and pathogens of community-acquired infections

CAIs are diseases that people contract outside of healthcare institutions. The introduction of infectious diseases into healthcare facilities from the service area has the potential to impact patient recovery and the health of healthcare workers. In addition, hospitals can be considered as potentially dangerous environments, as patients cared for due to CAIs can introduce various virulent pathogens into the hospital environment, thus they can be sources of epidemics. Moreover, patients admitted from the community are exposed not only to the endemic flora of the hospital, but also to pathogenic microorganisms carried by other patients. The most commonly detected CAIs are those due to enteric infections, respiratory tract infections and diseases caused by multidrug-resistant (MDR) bacteria.

1.3.1 Community-acquired enteric infections (gastroenteritis)

Diarrhoea of infectious origin, contracted in the community, is among the most prevalent communicable diseases worldwide and poses a significant public health concern. According to the Global Burden of Disease study (GBD), gastroenteritis is estimated to have resulted in 1.17 million deaths worldwide in 2021. The morbidity and mortality attributable to enteric pathogens are especially high among children under 5 years of age residing in low- and middle income countries. However, their importance is not negligible even in developed countries, as evidence shows that these infections are one of the most common causes of emergency department visits and hospitalizations in children. The main risk factors for enteric CAIs are malnutrition, pre-existing underlying diseases, immunocompromised status, cancer and poor hygienic conditions. The diagnosis of these infections is aided by the symptoms characteristic of the disease, but microbiological tests (faecal culture, antigen rapid test, polymerase chain reaction (PCR)) are necessary for an accurate diagnosis. In addition to symptomatic therapy, a number of antimicrobial agents can be used to treat this type of CAI. Vaccination is a potential preventive measure that is currently being used in certain cases, such as the vaccine against rotavirus infection. However, additional vaccines are under development, including those against norovirus infection.

<u>*The main pathogens of community-acquired enteric infections:*</u>

Among the pathogenic microorganisms that cause gastroenteritis, ***Salmonella*** species are one of the most important infectious agents that frequently cause enteric CAIs. Globally, enteric infections caused by *Salmonella* species are among the most commonly diagnosed foodborne illnesses, affecting people in all age groups. It is estimated that 94% of the 90 million cases of salmonellosis registered each year are attributable to the consumption of contaminated foods. Infection caused by this pathogen is associated with 155,000 deaths per year. Diseases due to *Salmonella* species are typically associated with gastrointestinal symptoms, and the infectious agent can be detected by stool culture. Antibiotics can be administered if indicated. However, it is important to note that the emergence of antibiotic-resistant strains is a growing problem. Additionally, individuals who are asymptomatic shedders or carriers of this pathogenic bacteria pose an additional risk to the health of the community, as they may facilitate the spread of infection.

Globally, in addition to *Salmonella* bacteria, ***Campylobacter jejuni and coli*** species are among the most common pathogens causing enteric CAIs. Foodborne infections caused by *Campylobacter* species, mainly due to the consumption of raw or undercooked meat (mainly poultry) or contaminated water, affect the health of 550 million people worldwide each year. Infections caused by the pathogen are most common in people over 75 years of age and children under 5 years of age. As with *Salmonella* infections, diseases due to *Campylobacter* species may be present with severe enteric symptoms, including bloody diarrhoea. Antibiotic therapy is available to treat the disease following identification of the pathogenic microorganism by laboratory testing, but resistance to certain drugs is becoming increasingly common in these species. A significant factor contributing to the community spread of *Campylobacter* species is the potential for asymptomatic shedding or carriage.

In addition to the bacterial species that have previously been discussed, ***Clostridioides difficile*** infection (CDI) is also a common cause of CAIs, but they are mainly related with healthcare-associated infections. Although the overall mortality associated with *C. difficile* is not particularly high when compared to other major communicable diseases, the infection was a leading cause of diarrhoea-related deaths in 2021. According to data published in the GBD, more than 15,000 deaths and almost 300,000 disability-adjusted life year (DALY) were attributed to CDI in the world in the same year. The growing public health importance of the infection is indicated by the doubling of the global DALYs attributable to CDI between 1990 and 2021 (from 1.83 to 3.46 per 100 000 people). Epidemiological studies have demonstrated an increase in the incidence of *C. difficile* infections in both adults and children. The progression of the disease is influenced by a number of factors, including age, the presence of underlying conditions (mainly intestinal diseases), antibiotic use and long-term hospitalization. The infection can be effectively treated with well-chosen antibiotic therapy. Various microbiological tests are available to identify the *C. difficile* bacterial species, but the most common and quickest method is the use of rapid tests to detect the toxins of the bacterium. Although *C. difficile* is a leading cause of healthcare-associated diarrhoea, the number of community-acquired cases has increased dramatically in recent years and it has been shown that 20-45% of CDI is due to community-acquired infections. Overuse and inappropriate use of antibiotics has been shown to be the main underlying cause.

In addition to pathogenic bacteria, viruses, including the highly contagious **rotavirus**, have been identified as the cause of acute diarrhoeal CAIs. Globally, rotavirus was estimated to be the leading cause of diarrhoeal death (15.2%) in 2021, with a high mortality in children under 5 years of age. According to the findings of an epidemiological study conducted in the European Union (EU), the prevalence of rotavirus-induced gastroenteritis among children under the age of 5 was estimated to be 15%. The study also found that the virus is particularly contagious in unvaccinated children under the 5 years of age, with an infection rate as high as 95%. The primary mode of transmission of this infection is through direct personal contact or contaminated liquids, food, hands and surfaces. The symptoms typically associated with the infection include fever and watery diarrhoea. Rapid antigen tests are available for the detection of the pathogen. The disease generally does not require specific treatment, symptomatic therapy, primarily the control of fever and adequate fluid replacement, is sufficient. However, in certain cases, hospitalization may be necessary due to the risk of severe dehydration. Therefore, it is recommended that the most at-risk population be vaccinated in order to prevent infection.

1.3.2 Community-acquired respiratory infections, severe acute respiratory infections

Community-acquired lower and upper respiratory tract infections are of major clinical importance and are among the most common infectious diseases. In 2021, upper respiratory tract infections were estimated to cause 19 600 deaths worldwide (0.2 deaths/100 000 population). Although mortality from upper respiratory tract infections is relatively low, it is important to note that they can lead to severe lower respiratory tract infections (LRIs), which are associated with much higher mortality rates. According to the GBD, the number of LRIs worldwide was 344 million (4,350 new cases/100,000 population), with an estimated 2.18 million associated deaths (27.7 deaths/100,000 population) in 2021. The main risk factors contributing to the development and progression of CAIs are age, smoking, immunosuppression, the presence of certain underlying chronic diseases (coronary heart disease, respiratory diseases) and poor social and hygienic conditions. In addition to the detection of specific symptoms and physical examination, a variety of rapid diagnostic methods (rapid tests, PCR) are available to detect respiratory CAIs. These diseases can be treated with antibiotics and antivirals if indicated. Some of these CAIs can be prevented by vaccination.

Among respiratory CAIs, severe acute respiratory infections (SARIs) are of greatest clinical importance. SARI is defined by the World Health Organisation (WHO) as "an acute respiratory illness leading to hospitalization and characterized by cough and fever equal to or higher than 38°C developed no longer than 10 days before admission". These infections are a significant cause of hospital admissions in many countries. Complications arising from the infection, including pneumonia and bronchiolitis, are associated with a high mortality rate in children under five. Although global estimates of the morbidity and mortality caused by SARIs in children are not available, the number of LRIs, which include SARIs, in children under five worldwide was 37.8 million (5750 new cases/100 000 population), and infections were responsible for 0.5 million deaths (76.2 deaths/100 000 population) in 2021. The most commonly identified etiological agents of SARIs in children are severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza viruses (type A, B) and respiratory syncytial virus (RSV).

The most important pathogens for community-acquired severe acute respiratory infections:
Since its identification in 2020, the **SARS-CoV-2** virus has been regarded as one of the pathogenic microorganisms that can cause SARI in children. According to the findings of epidemiological studies, between 1-6% of cases of SARS-CoV-2 were reported in children under the age of 15. Although they may present with a milder form of the infection than adults, the adverse effects of the disease in younger age groups are not negligible. It has been reported that children infected with SARS-CoV-2 frequently exhibit symptoms including high fever, respiratory symptoms such as cough and sore throat, and enteric symptoms such as diarrhoea and vomiting. SARS-CoV-2 often affects the upper respiratory tract and subsequently can cause severe, even fatal, LRI.

In addition to the infection caused by the novel coronavirus, seasonal **influenza A and B** viruses, which also frequently cause SARI, represent a significant public health concern. It was estimated that influenza caused 14.4 million infections worldwide in 2021, of which 3-5 million cases were classified as severe. The WHO has reported that more than 100,000 deaths worldwide have been attributed to influenza virus infections. The analysis also demonstrated that the highest rates of hospitalization and mortality were observed among children under 5 years of age and adults aged 65 and above. In accordance with the findings of the study, a comprehensive analysis of data on influenza infections from 40 countries and administrative regions identified that the rates of hospitalization for children under 5 and adults aged 65 and above per 100,000 individuals were 224.0 and 96.8, respectively. The primary reasons for hospitalization of patients infected with the influenza virus are the development of infection-related complications. For instance, influenza viruses were identified as the causative agent in 9% of european patients hospitalized with pneumonia.

RSV is one of the respiratory pathogens that commonly cause CAIs, particularly in children. Although global data on SARI caused by the virus are not available, the importance of the infection is illustrated by the fact that RSV was estimated to cause 4.59 million LRIs and more than 30 000 deaths worldwide in 2021. Results from hospital-based studies have shown that RSV is a common cause of hospitalization in children under 5 years of age with LRI. According to a systematic analysis by Li and colleagues, 33 million RSV-related LRIs occurred in this age group globally in 2019. The authors also found that RSV-associated LRIs were responsible for 3.6 million hospitalizations and 26,300 deaths in children under 5 years of age. In addition, it was described that 39% of hospitalizations and 51% of deaths occurred in children under 6 months of age.

1.3.3 Community-acquired infections due to multidrug-resistant bacteria

Diseases caused by community-acquired MDR bacteria are also classified as CAIs. The pathogens responsible for these infections are classified as MDR microorganisms, defined as organisms that are resistant to at least three different classes of antimicrobial agent. Although MDR bacteria are generally identified as the pathogens responsible for nosocomial infections, their spread within the community can contribute to increased morbidity and mortality in susceptible populations. According to the EU Antimicrobial Resistance Surveillance Report, the estimated number of community- and healthcare-associated MDR infections in this region was 670,000, and the number of associated deaths was 33,000 in 2020. The spread of MDR bacteria has been demonstrated to be associated with the misuse or overuse of antibiotics, which can result in the emergence of antimicrobial resistance (AMR). Infections caused by antibiotic-resistant bacteria are considered to be among the most significant challenges to global health. The significance of AMR is further compounded by its potential to occur in any country and to affect any individual, irrespective of age or gender.

Epidemiological studies have demonstrated that the incidence of MDR-related morbidity and mortality is highest in intensive care units, partly due to the severe clinical condition of patients and the frequent use of antibiotics. A study conducted for the member states of the EU/European

Economic Area (EEA) found that the incidence of infections and associated mortality per 100,000 population, along with the overall burden of disease related to antibiotic-resistant bacteria, showed a substantial increase between 2016 and 2020. According to another estimate, using data from the same countries, the DALYs associated with MDR bacterial infections (170 DALYs per 100,000 population) in 2015 were almost equivalent to the combined burden of disease from influenza, tuberculosis and HIV/AIDS (183 DALYs per 100,000 population). MDR bacteria present a significant challenge to health systems, due to their ability to cause serious and difficult-to-treat infections, as well as to increase the length of hospital stay, treatment costs and mortality rates, particularly among the elderly. Another key concern is the increasing incidence of colonisation with MDR bacteria, which contributes to the spread of this pathogen within the community. The most prevalent CAIs associated with MDR bacteria are respiratory, urinary, wound, skin, soft tissue and bloodstream infections.

The most frequent multidrug-resistant bacteria causing community-acquired infections:

The results of the available studies provide only limited information on the epidemiology of CAIs caused by MDR bacteria. Data on CAIs due to MDR bacteria are usually reported jointly with the HAIs. Consequently, the bacterial species specific results presented in this paragraph refer to CAIs and HAIs together.

One of the most commonly detected MDR bacteria causing CAIs is **methicillin-resistant *Staphylococcus aureus* (MRSA)**. MRSA is one of the pathogenic microorganism that, due to its high resistance to penicillin (90% of *S. aureus* isolates are penicillin resistant), causes a significant public health problem even in areas where it is present only in a small proportion of the population. The European Centre for Disease Prevention and Control (ECDC) has reported that 15.8% of *S. aureus* isolates were methicillin-resistant in 2021. A recent survey of 135 countries found that *S. aureus* infections are among the leading causes of death from pathogenic bacteria, accounting for the highest number of deaths in people aged 15 years and older worldwide. MRSA is primarily responsible for causing respiratory tract, skin and soft tissue infections. However, it can also infect heart valves, lungs, bones or joints when it enters the bloodstream. In addition, MRSA is one of the pathogens that often leads to colonisation of the respiratory tract, which can facilitate the spread of the pathogenic microorganism in the community.

Multidrug-resistant *Escherichia coli* (MECO) has been identified as a leading cause of CAIs caused by MDR bacteria. According to a report of the ECDC in 2021, in half of the countries providing data on *E. coli*, at least 25% of samples showed resistance to some classes of antibiotics. *E. coli* isolates are often resistant to fluoroquinolones and third-generation cephalosporins. MECO is a major cause of community-acquired urinary tract and bloodstream infections.

CAIs associated with MDRs are often caused by **multidrug-resistant *Klebsiella* species (MKLE)**, of which *K. pneumoniae* is of greatest clinical importance. This microorganism is also resistant to a wide range of antibiotics. Antibiotic resistance was detected in almost half of the EU Member States providing data on *K. pneumoniae* isolates, in 50% of samples, in some cases it was even higher. In the WHO European Region, resistance to carbapenems and third-generation cephalosporins is the most common in *K. pneumoniae* isolates. MKLE is frequently detected as the causative agent of community-acquired pneumonia and urinary tract infections causing serious complications (e.g. sepsis).

Although **multidrug-resistant *Pseudomonas aeruginosa* (MPAE)** is less frequently identified as a cause of CAIs than the above-mentioned MDR bacteria, its clinical importance cannot be overlooked, as it is resistant to many antibiotics and represents a significant challenge in healthcare settings. The resistance of *P. aeruginosa* to carbapenems is a significant problem, which is reportedly increasing in EU/EEA Member States. MPAE has been identified as a primary cause of community-acquired pneumonia and can lead to urinary tract and bloodstream infections.

As with MPAE, **multidrug-resistant *Acinetobacter baumannii* (MACI)** is predominantly identified as the causative agent of healthcare-associated infections; however, in certain cases, it has also been linked to the development of CAIs. There is an increasing concern regarding the antibiotic resistance of *A. baumannii*, as highlighted in the ECDC AMR surveillance report. According to data in the publication, the share of carbapenem resistant isolates were 50% or greater in more than half of the countries included in the analysis in 2021. MACI is predominantly associated with community-acquired pneumonia, skin and soft tissue infections.

Among MDR bacteria, **vancomycin-resistant *Enterococcus* species (VRE)** rarely cause CAIs. The clinically most relevant species are vancomycin-resistant *E. faecium* and *E. faecalis*. The ECDC found that in a quarter of countries reporting data on *E. faecium* isolates, resistance was detected in at least 25% of samples. Although VRE is primarily associated with nosocomial infections, it has also been identified as an infectious agent in community-acquired diseases (wound infections) where the pathogenic microorganism originates from the human environment (herbs used for wound treatment). It has also been described that VRE can cause colonisation. Taken together, these findings suggest that the community transmission of VRE is not negligible.

Although in a smaller number of cases than the MDR species discussed above, **multidrug-resistant *Enterobacter* species (MENB)** can also cause CAIs. The majority of *Enterobacter* isolates exhibit extensive resistance to fluoroquinolones, penicillins and third-generation cephalosporins, as these antibiotic classes are frequently used in the treatment of infections. Of the MENBs, *E. cloacae* and *E. hormaechei* species are of the greatest clinical importance and can cause primarily community-acquired urinary tract infections.

In addition to MENB, **multidrug-resistant *Stenotrophomonas maltophilia* (MSTM)** is one of the lesser known drug-resistant bacteria that can cause therapeutically challenging CAIs, including respiratory, urinary tract and bloodstream infections.

The most common type of CAI caused by MDR bacteria is community-acquired urinary tract infection, which can also be caused by **other multidrug-resistant species** such as ***Proteus mirabilis***, ***Citrobacter freundii*** and ***Morganella morganii***.

2 AIMS OF THE STUDY

As CAIs caused by enteric pathogens, influenza viruses and MDR bacteria have become more common, the number of complications and deaths related to them has also increased. To prevent CAI-associated morbidity and mortality, information is needed on the characteristics of patients hospitalized with these diseases and factors affecting their condition. However, there are only a few studies on the epidemiology of patients with CAI. The investigations available have found that CAIs due to MDR bacteria were the most frequent among the elderly, whereas community-acquired influenza and enteric diseases affected both children (under 5 years) and elderly (60 years old or older). In addition, previous studies have suggested that there can be differences in the spread of pathogenic microorganisms causing CAI between the population living in urban and rural areas. However, data on the share of patients with CAI due to enteric pathogens, influenza viruses and MDR bacteria living in settlements with different characteristics are limited, even in developed countries. It has also been shown that the length of hospital stay is increased if the patients suffered from CAI caused by enteric pathogens, influenza viruses or MDR bacteria. In addition, there is an association between the length of hospital stay and mortality among patients with CAI. However, there is no study that simultaneously investigated which of these diseases can result in the longest hospital stay and the highest mortality among patients with CAI. To identify factors influencing the length of hospital stay for patients with CAI, only a few epidemiological investigations have developed regression models focusing mainly on community-acquired pneumonia. According to our knowledge, there are no studies using regression analysis that report which type of CAIs and patient characteristics have the greatest influence on the length of hospital stay.

1. One of the aims of our study was to collect data on the characteristics of patients with CAIs treated for enteric pathogens, influenza viruses and MDR bacteria from a Hungarian university hospital and to perform a descriptive statistical analysis based on this data.

2. We also aimed to investigate whether there is a difference in the proportion of patients with CAI by the patient's place of residence and determining which of the diseases can result in the longest hospital stay and the highest mortality.

3. The third aim of our study was to develop a regression model to identify factors that influence the length of hospital stay of patients with CAI.

Several studies have shown that SARS-CoV-2, influenza and RSV are the most frequently detected respiratory pathogens that cause SARI in children. However, only a few studies have compared the characteristics of SARI due to these viruses in paediatric patients. In addition, there have been only a limited number of investigations that have provided data on patients and studied the factors affecting disease severity and length of hospitalization. According to our knowledge, there are no studies in the scientific literature that have used comprehensive statistical analyses to identify which of the respiratory infections and patient characteristics have a significant impact on the duration of hospital stay in children with SARI. To fill this gap, we have processed data from children treated in a Hungarian university hospital with SARS-CoV-2, influenza A and RSV-associated SARI.

4. The primary goal of our research was to demonstrate the characteristics of patients treated with SARI using descriptive statistical methods.

5. We also aimed to compare the length of hospitalization among patients diagnosed with SARI due to the respiratory viruses investigated.

6. The third objective of our research was to identify factors that influence the duration of hospitalization in children with SARI.

3 DATA AND METHODS

3.1 Comparison of length of hospital stay for community-acquired infections due to enteric pathogens, influenza viruses and multidrug-resistant bacteria

3.1.1 Location, time period and type of the study

A cross-sectional study was conducted covering the University of Debrecen Clinical Centre Nagyerdei Campus (UDCC NC), Hungary from 1 January to 31 December 2020.

3.1.2 Data sources

To identify patients with CAI, data on laboratory-confirmed infections were retrieved from the Medbacter microbiology information system of the UDCC NC for the period between 1 January and 31 December, 2020. Next, the date of admission for each patient was obtained from the e MedSolution medical information system of the UDCC NC. An infection was considered to be community-acquired when it was clinically evident at the time of hospital admission or diagnosed within 48 hours of hospital admission without any previous encounter with healthcare. Subsequently, the following data were obtained for each patient from the e-MedSolution medical information system: age, sex, place of residence, time of admission and discharge, hospital ward (place of treatment), time of sampling, test material (respiratory, wound, hemoculture, urine and stool sample), microbiological result and previous antibiotic use. The patients' place of residence was categorized as 'village', 'city' and 'cities with county status' according to the classification system of the Hungarian Central Statistical Office. 'Village' is defined as a settlement which has its own individual identity separate from other settlements, and its legal status is other than a town. Settlements are categorized as 'cities' if they have some central role in the geographical division of labor, and they are typically not agricultural settlements and have the legal status of a city. Cities with county status are settlements designated by the respective legal rule as the seat of the county. The total number of inpatients treated at the UDCC NC in 2020 was obtained from reports of the Department of Medical Documentation of the University of Debrecen. We had ethical approval from the Regional and Institutional Ethics Committee of the University of Debrecen to process patient data (DE RKEB/IKEB: 5677-2021).

3.1.3 Inclusion and exclusion criteria for selection of patients with community-acquired infections

Our study included inpatients with CAI due to enteric pathogens, influenza viruses and MDR bacteria. However, patients with coronavirus infections, colonisation and CAI other than those included in this study were excluded from our research. In addition, outpatients were also omitted from our study.

3.1.4 Database development

The number of infections meeting the criteria of CAI was 2116 in the UDCC NC for the period studied. Coronavirus infections were not included in our database because we intended to analyze data on other major causes of CAI. Therefore, patients with coronavirus infections (n = 1118), colonisation (n = 177) and CAI other than those included in this study (n = 122) were excluded from our database. This left 699 patients with CAI infection in our database. Then, patients with CAI treated at outpatient level (n = 168) were also omitted from our database. As a result, 531 patients with CAI remained in our database including enteric (n = 197) and influenza virus (n = 71) infections and diseases caused by MDR bacteria (n = 263). Enteric infections included illnesses caused by *Campylobacter jejuni*, *Campylobacter coli*, *Salmonella* species, *C. difficile* (CDI) and Rotavirus. Respiratory diseases by Influenza A and B viruses were included in the category of Influenza virus infections. Diseases caused by the following pathogenic microorganisms were categorized as infections by MDR bacteria: Methicillin-resistant *Staphylococcus aureus* (MRSA), MDR *Escherichia coli* (MECO), MDR *Klebsiella* species, (MKLE), MDR *Pseudomonas aeruginosa* (MPAE), MDR *Acinetobacter baumannii* (MACI), MDR *Enterobacter* species (MENB), MDR *Stenotrophomonas maltophilia* (MSTM), other MDR species (*Proteus mirabilis, Citrobacter freundii, Morganella morganii*, MR Other) and Vancomycin-resistant *Enterococcus* species (VRE).

3.1.5 Statistical analysis

To characterize the sample population, the proportion of patients with CAI was calculated by gender, 10-year age groups, previous antibiotic use, place of residence, causes of CAI and outcome of illnesses. The percentage of patients with CAI was also determined by the type of CAI and place of treatment (hospital ward). To determine the number of patients with CAI per 100,000 inpatients at the UDCC NC in 2020, the number of patients with each type of CAI was divided separately by the total number of inpatients treated at the UDCC NC in 2020 and multiplied by 100,000. Then, the number of days of care was calculated for each patient with

CAI. Subsequently, the median length of hospital stay and the corresponding interquartile ranges (IQR) were calculated separately for patients with CAI by enteric pathogens, influenza viruses and MDR bacteria. To determine whether there is a difference between the length of hospital stay of patients with these CAIs, we used the Kruskal–Wallis test with the Bonferroni post-hoc test. To show which patients had the longest hospital stay among the CAI types included in our study, the median number of days of care and the corresponding IQR were calculated separately for each type of CAI. Next, we applied the Chi-square and the Fischer exact test to determine whether there is a difference within each type of CAI in the proportion of patients by the patient's place of residence. Then, cases with CAI were divided into two groups based on the median length of hospital stay of all patients with CAI. Group 1 and group 2 included patients for whom the duration of hospitalization was less than or equal to the median and more than the median, respectively. The Chi-square test or the Fischer exact test were applied for each type of CAI separately to see whether there is a difference between the proportions of patients whose care lasted fewer and more days than the median hospital stay of all patients with CAI. To identify factors that influence the length of hospital stay for patients with CAI, we developed a multiple binary logistic regression model. The dependent variable in the logistic regression model was the median number of days of care (≤median; median<), and the independent variables were the patient's sex and age, place of residence, type of CAI, and place of treatment (hospital ward). Logistic regression was performed using the forced entry method. Variables were included in the initial model if there was an association with length of hospital stay in the scientific literature or the univariate analysis showed a statistically significant relationship between them. The final model included gender as a general confounder. Regression analysis included only those types of CAI and hospital wards which had at least 15 and 13 patients, respectively. The model fit was assessed using Nagelkerke R^2. The results were considered to be statistically significant when $p < 0.05$. Statistical analyses were performed using IBM SPSS version 28.0.1 (IBM Inc, Armonk, New York, NY, USA).

3.2 Comparison of the clinical characteristics of children with severe acute respiratory infections by cross-sectional study

3.2.1 Study design and sampling

A cross-sectional study was conducted at the UDCC NC in Hungary from the 40^{th} week of 2021 to the 20^{th} week of 2022 (from October 4^{th}, 2021 to May 22^{nd}, 2022). Our study collected data on patients infected with SARS-CoV-2, influenza and RSV. All children admitted to the hospital with respiratory symptoms were tested for SARS-CoV-2 infection with a rapid antigen test (RAT). In addition, a nasopharyngeal sample was obtained for PCR testing from children with a positive coronavirus RAT result and clinical symptoms suggesting the presence of Influenza A/B or RSV co-infection. When the coronavirus RAT yielded a negative result, an RSV RAT was performed. Patients whose result was negative for both viruses were subject to further testing for infections with other respiratory viruses using a PCR analysis.

3.2.2 Acquisition of patient data

To identify individuals with SARI, we retrieved data on infections of SARS-CoV-2, influenza, and RSV from the Medbacter and UD MED IT systems of the UDCC NC. These systems provide detailed information on microbiological test results and patients' anamnesis. The period of data collection was from the 40th week of 2021 to the 20th week of 2022. Medical information collected for each patient included age, sex, place of residence, date of admission and discharge, place of treatment (hospital ward), date of sampling, type of specimen, microbiological result, and underlying diseases. In addition, information related to the therapy of the patients were also collected including the presence or absence of pneumonia, mechanical ventilation and oxygen therapy. Next, patient records were reviewed and those matching the case definition of SARI (cough and fever ≥ 38 °C developed no longer than 10 days before admission) were obtained for further analysis. Subsequently, SARI cases with positive test result for SARS-CoV-2, influenza and RSV infection were included in our study. Last, the underlying diseases of the selected SARI patients were classified into illness categories using the 10th revision of International Classification of the Diseases.

To process patient data, ethical approval was obtained from the Regional and Institutional Ethics Committee of the University of Debrecen (DE RKEB/IKEB: 5677 − 2021).

3.2.3 Database development

The total number of inpatients with SARI was 1464 in our study. Adult patients were excluded from our database as our study concentrated exclusively on children with SARI. Therefore, adults infected with SARS-CoV-2 (n = 734) and influenza (n = 17) viruses were not included in our database. There were no cases of RSV infection among adults. Consequently, our database comprised data on 713 children with SARI due to SARS-CoV-2, influenza A and RSV infections. Patients with influenza B or C virus were not detected. Apart from the respiratory viruses investigated, no other pathogen causing SARI in children was detected in our sample. All children with SARI were treated at the Department of Paediatrics of the UDCC NC.

3.2.4 Statistical analysis

To examine the temporal distribution of infections investigated, the number of weekly cases was divided by the number of children hospitalized each week at the Department of Paediatrics for the period between the 40^{th} week of 2021 and the 20^{th} week of 2022. The results were expressed as the weekly number of cases per 1000 inpatients. The weekly number of inpatients at the Department of Paediatrics was retrieved from data reported by the Department of Medical Documentation of the UDCC NC. First, a descriptive statistical analysis was conducted to determine the share of children with SARS-CoV-2, influenza A and RSV infections. The percentage of children was also calculated by gender, age groups, factors indicating the severity of the disease (intensive care, pneumonia, mechanical ventilation, oxygen therapy and underlying disease) and outcome of illness. Next, the duration of care for each child with SARI was computed. Then, the median duration of hospitalization and corresponding IQR were calculated separately for children with SARS-CoV-2, influenza A and RSV infections. Prior to performing group comparisons, data was assessed for normality by the Shapiro-Wilk test and found to be not normally distributed. We performed a Kruskal-Wallis test with Bonferroni post hoc analysis to examine whether there is a difference in the length of hospitalization in children with the respiratory infections investigated. A multiple logistic regression model was developed to identify factors that can affect the duration of care for children with SARI. The regression model included the median number of days of care as a dependent variable (<median; median≤). Independent variables were sex, age, type of infection, and factors indicating disease severity such as intensive care, pneumonia, mechanical ventilation/oxygen therapy and underlying diseases. Logistic regression analysis was carried out using the forced entry procedure. Variables were incorporated into the initial model if the univariate analysis indicated a statistically significant association among them. Gender and age were included as general confounding variables in the final model. Results with p values less than 0.05 were considered statistically significant. IBM SPSS version 28.0.1 (IBM Inc, Armonk, New York, NY, USA) was used to carry out statistical analyses.

4 RESULTS

4.1 Comparison of length of hospital stay for community-acquired infections due to enteric pathogens, influenza viruses and multidrug-resistant bacteria

4.1.1 Characteristics of patients with community-acquired infections

The number of males and females were 256 (48.21%) and 275 (51.79%) among patients with CAI, respectively. It is also demonstrated that the largest proportion of patients with CAI originated from the age groups of 0–9 (32.96%, n = 175), 60–69 (14.31%, n = 76), 70–79 (16.76%, n = 89), and 80–89 (16.57%, n = 88) years. The mean age ± standard deviation (SD) of all the patients with CAI was 46.68 ± 34.48 years. When taking into account the age of patients with CAI separately by enteric pathogens, influenza viruses and MDR bacteria, the mean age ± SD was found to be 22.79 ± 31.30 years, 29.09 ± 29.58 years and 69.32 ± 20.27 years, respectively. Previous antibiotic use in the past 30 days was recorded in 10 cases (1.88%). In addition, CAIs included in this study were detected more frequently among patients living in cities with county status (46.52%) than among those living in other types of settlement. MDR bacteria were found to be to the cause of CAI in 49.53% of the patients included in this study. The in-hospital mortality was the highest among patients with CAI due to MDR bacteria (26.24%), however, 83.24% of patients with CAI recovered from the disease.

4.1.2 Distribution of community-acquired infections by pathogens and by hospital wards

Of the enteric pathogens studied, *Salmonella species* (n = 62, 31.47%, 86.76 cases/100,000 inpatients) were the most frequent cause of gastroenteritis at the UDCC NC in 2020. The number of patients with Influenza virus infection was 99.35/100,000 inpatients (n = 71). Among the MDR bacteria MECO (n = 102, 38.78%, 142.73 cases/100,000 inpatients) caused the highest number of infections. The patients with CAI were detected most frequently at hospital wards of Paediatrics (n = 192, 36.16%) and General medicine A (n = 106, 19.96%) and B (n = 111, 20.90%).

4.1.3 Distribution of length of hospital stay of patients with community-acquired gastroenteritis, influenza and multidrug-resistant bacterial infections

The length of hospital stay of patients with MDR bacterial infection was significantly longer than that of patients with gastroenteritis ($p < 0.001$) and influenza ($p < 0.05$).

4.1.4 Number of days of care of patients with community-acquired infections by pathogens

Considering the duration of hospital stay of all patients with CAI, the median number of days of care was 6 (IQR: 2–10). Among the CAI types studied, patients with MPAE (median: 11 days, IQR: 2.5–19.5) and Rotavirus infection (median: 3 days, IQR: 2.5–3.5) had the longest and shortest hospital stay, respectively.

4.1.5 Distribution of length of hospital stay among patients with community-acquired infections

The proportions of patients with CDI ($p < 0.01$), MECO ($p < 0.001$) and MKLE ($p < 0.001$) infections hospitalized for more than 6 days were significantly larger than those of cases treated for 6 or less days. In contrast, compared with the percentage of patients with *Campylobacter* ($p < 0.001$), *Salmonella* ($p < 0.001$) and Rotavirus ($p < 0.001$) infections treated for more than 6 days, the proportions of cases with those diseases hospitalized for 6 or less days were significantly larger.

4.1.6 Distribution of community-acquired infections by the patients' place of residence

Compared with cases with *Campylobacter* and Rotavirus infection living in cities with county status, significantly larger proportions of patients with those diseases were from villages (*Campylobacter*: $p < 0.01$, Rotavirus: $p < 0.001$) and cities (*Campylobacter*: $p < 0.01$, Rotavirus: $p < 0.001$). Furthermore, a significantly larger percentages of patients with MECO and MKLE ($p < 0.05$) infections were from cities with county status than from villages and cities.

4.1.7 Significant influencing factors of hospital stays longer than 6 days for patients with community-acquired infections based on multiple logistic regression model

Multiple binary logistic regression analysis showed that CDI (odds ratio (OR): 6.98, 95% confidence interval (CI): 1.03–47.48; $p = 0.047$), MECO (OR: 7.64, 95% CI: 1.24–47.17; $p = 0.029$) and MKLE (OR: 7.35, 95% CI: 1.15–47.07; $p = 0.035$) infections were independent risk factors for hospital stays longer than 6 days. The hospitalization at departments of pulmonology

(OR: 5.48, 95% CI: 1.38–21.76; p = 0.016) and surgery (OR: 4.19, 95% CI: 1.18–14.81; p = 0.026) increased the odds of hospital stays longer than 6 days. On the other hand, female sex (OR: 0.62, 95% CI: 0.40–0.97; p = 0.037) and hospitalization at departments of paediatrics (OR: 0.17, 95% CI: 0.04–0.64; p = 0.009) decreased the odds of hospital stays longer than 6 days. The Nagelkerke R^2 for the model was found to be 0.435.

4.2 Comparison of the clinical characteristics of children with severe acute respiratory infections by cross-sectional study

4.2.1 Characteristics of children with severe acute respiratory infection by SARS-CoV-2, influenza A virus and RSV

The proportion of children with SARS-CoV-2, influenza A and RSV was 76.58% (*n* = 546), 6.17% (*n* = 44) and 17.25% (*n* = 123), respectively. It was also found that the share of boys and girls with SARS-CoV-2 (54.58%; 45.42%), influenza A (52.27%; 47.73%) and RSV (47.97%; 52.03%) infection was similar. The mean age ± SD of children diagnosed with SARS-CoV-2, influenza A and RSV infection was 3.47 ± 5.14 years, 5.41 ± 4.35 years and 0.12 ± 0.52 years, respectively. Analysis of data showed that patients with SARI between 1 and 6 years (30.43%, *n* = 217) and under 1 year of age (51.75%, *n* = 369) were present in the largest proportion in our sample. In addition, infants under 1 year of age had the highest share among cases infected with SARS-CoV-2 (45.79%, *n* = 250) and RSV (93.50%, *n* = 115). In contrast, the proportion of paediatric patients between 1 and 6 years of age was the largest among children with influenza A virus (65.91%, *n* = 29). The proportion of cases requiring intensive care (8.94%), mechanical ventilation (8.94%) or oxygen therapy (13.01%) was the highest among those with SARI due to RSV. Furthermore, pneumonia (29.27%) was the most frequent among children with this infection. The proportion of children with underlying illnesses were 15.02%, 2.27% and 4.88% among cases infected by SARS-CoV-2, influenza A and RSV, respectively. There was no in-hospital mortality in children with influenza A and RSV infection. However, two patients with SARS-CoV-2 infection (0.37%) died. Considering all children with SARI, the median length of care was 4 days (IQR: 3–5 days). The patients infected with RSV had the longest hospitalization with a median of 5 days (IQR: 4–7 days). Our analysis also demonstrated that the median length of hospitalization was the same (4 days) among children with SARI due to SARS-CoV-2 and influenza A infection.

4.2.2 Underlying diseases among children with severe acute respiratory infection caused by SARS-CoV-2, influenza A virus and RSV

The category of the diseases of the respiratory system including allergy, asthma and lung disease had the highest proportion (20%). In addition, asthma (17%), mental retardation (14%), obesity (10%) and prematurity (10%) were the most common underlying diseases in paediatric patients.

4.2.3 Temporal distribution of severe acute respiratory infections due to SARS-CoV-2, influenza A virus and RSV cases per 1000 inpatients

The number of new SARS-CoV-2, influenza A and RSV cases per 1000 inpatients was the highest on the 4^{th} week of 2022 (118.11 SARS-CoV-2 cases/1000 inpatients), the 8^{th} week of 2022 (27.30 influenza A cases/1000 inpatients) and the 44^{th} week of 2021 (45.48 RSV cases/1000 inpatients), respectively.

4.2.4 Age distribution of children with severe acute respiratory infections caused by SARS-CoV-2, influenza A virus and RSV

In our research, we detected a significant difference in the age distribution of paediatric patients infected with SARS-CoV-2, influenza A and RSV ($p < 0.001$).

4.2.5 Distribution of length of hospitalization in children with severe acute respiratory infections due to SARS-CoV-2, influenza A virus and RSV

The duration of care for cases with RSV ($p < 0.001$) was significantly longer when compared to that of in children with SARS-CoV-2 and influenza A infection.

4.2.6 Factors influencing the length of hospital stay in children with severe acute respiratory infection based on a multiple logistic regression model

Our regression model showed that RSV infection (OR: 3.25, 95% CI: 1.43–7.38; $p = 0.005$) and pneumonia (OR: 3.65, 95% CI: 2.14–6.24; $p < 0.001$) significantly increased the odds of hospitalization longer than 4 days. Furthermore, the patients requiring mechanical ventilation or oxygen therapy (OR: 3.23, 95% CI: 1.29–8.11; $p = 0.012$) and cases with underlying illnesses (OR: 2.39, 95% CI: 1.35–4.23; $p = 0.003$) had significantly higher odds for inpatient care longer than 4 days.

5 DISCUSSION

5.1 Comparison of length of hospital stay for community-acquired infections due to enteric pathogens, influenza viruses and multidrug-resistant bacteria

Community-acquired infectious diseases can increase the risk of complications, thereby often resulting in longer hospital stays for patients with these illnesses. In addition, mortality has been shown to be increased among patients with CAI. However, it has not been previously known which of type of CAI can result in the longest hospital stay and the highest mortality. Factors influencing the length of hospital stay of patients with CAI due to enteric pathogens, influenza viruses and MDR bacteria have also not been investigated. To fill this knowledge gap, we obtained data on 531 patients with CAI from the medical databases of UDCC NC then used them to analyze patient characteristics and develop a regression model. Our results showed that compared with cases with *Campylobacter* and Rotavirus infection living in cities with county status, significantly larger proportions of patients with those diseases were from villages and cities. In addition, significantly larger percentages of patients with MECO and MKLE infections were from cities with county status than from villages and cities. We also found that patients with MDR bacterial infection had the highest mortality (26.24%) and they stayed significantly longer in hospitals than cases with other types of CAIs. Of the CAIs by MDR bacteria, infections due to MECO were shown to be the most frequent (n = 102, 38.78%, 142.73 cases/100,000 inpatients). Considering all patients with CAI, the median length of hospital stay was found to be 6 days. Our study showed that among the patients with CAI, those with MPAE and Rotavirus infections had the longest (median: 11 days) and the shortest (median: 3 days) hospital stay, respectively. In addition, it was demonstrated that hospitalization for more than 6 days was significantly more frequent among patients with CDI, and infections by MECO and MKLE. Using multiple logistic regression, we have identified five and two factors that significantly increased (CAI by CDI, MECO and MKLE, hospitalization at department of pulmonology and surgery) and decreased (female sex, hospitalization at department of paediatrics) the odds of staying in the hospital for more than 6 days, respectively.

Prior investigations have reported that the spread of pathogenic microorganisms causing CAI can be facilitated by the urban environment including densely built city centers, crowded public transportation and close contact with companion animals such as dogs and cats. Therefore, it is assumed that people's place of residence can influence the type of pathogenic microorganisms they are exposed to on a daily basis. This might contribute to differences in the share of patients with CAI due to enteric pathogens, influenza viruses and MDR bacteria in villages, cities, and cities with county status. Our results support this assumption for CAI due to *Campylobacter*, Rotavirus, MECO and MKLE; however, further research is required to determine the role of environment at a settlement in the spread of CAIs.

Previous epidemiological studies have shown that CAI due to MDR bacteria can result in long hospital stays and high mortality of patients. Our results confirmed these findings, demonstrating that mortality from MDR bacterial infection was more than twice and four times higher than that of from influenza virus infection and gastroenteritis, respectively. In addition, the median number of days of care of patients with MDR bacterial infection was 2.0 and 1.6 times higher than for cases with gastroenteritis and influenza, respectively. The results obtained could be due the differences in the age of patients since advanced age has been identified as one of the major risk factors for mortality from MDR infections. This possible explanation is also supported by the results of our investigation, as the mean age of patients with MDR bacterial infection was more than twice of the cases with gastroenteritis and influenza. Therefore, among CAI, MDR infections should be considered as a public health priority in populations vulnerable to them.

To determine how the median length of hospital stays of patients with MPAE infection in our study relates to those described in previous research, we compared our results with the existing evidence. According to two recent publications from the United States of America (USA) and Australia, the median length of hospital stay of patients with MPAE infections was 8 days which is in accordance with our results (median: 11 days). The reason for the long hospital stays of these patients can be related to complications including pneumonia and bacteremia that often develop as a result of MPAE infection. Clinical studies have shown that delayed identification of MPAE infection associated pneumonia can increase not only the duration of care, but also its treatment cost and mortality. Therefore, the early detection of the disease followed by therapy with adequate antibiotics is essential to decrease the burden related to CAI by MPAE.

Similar to CAI due to MPAE, infections with *C. difficile*, MECO and MKLE are often associated with severe diseases such as diarrhoea, urinary tract infections, and blood stream infections. Previous studies have shown that a large proportion of patients with these illnesses have pre-existing risk factors including smoking, high blood glucose levels, high body mass index, previous antibiotic use and advanced age. Although, data on risk factors for cases with *C. difficile*, MECO and MKLE infections were not available in our study, we hypothesize that they may have contributed to the higher proportion of hospitalization for more than 6 days among these patients. Our results indicate that further research is needed to determine the effects of pre-existing risk factors on the length of hospitalization for patients with community-acquired *C. difficile*, MECO and MKLE infections.

The results of our regression model suggest that the length of hospital stay can depend on the health status of the patients. Compared with patients without comorbidities, the duration of recovery from CAIs is longer for those with immunosuppression, cancer and chronic respiratory diseases. Previous studies have shown that differences in health and lifestyle among men and women in combination with CAI can lead to longer hospital stays. In addition, it has been reported that in males, infections are at a more advanced stage when they are admitted to hospital, further increasing the length of hospitalization. This is consistent with the results of our regression analysis, which showed that women are 0.38 times less likely than men to stay in the hospital for more than 6 days. Following the same logic, it is assumed that *C. difficile*, MECO and MKLE infections independently increase the odds of hospital stays longer than 6 days because patients with these infections often admitted with poor health and comorbidities. Patients admitted with comorbidities are not evenly distributed between hospital wards, those with cancer and chronic respiratory diseases can be present in a much larger proportions among adults in pulmonology and surgery units than among children in the paediatric ward. Therefore, patients with CAI treated in pulmonology and surgery wards have 5.48 and 4.19 times higher odds, respectively, of being hospitalized for more than 6 days compared with CAI patients treated in other units.

The strengths and limitations of this study should be considered. This is the first study that compares the characteristics of patients with different types of CAI in the same university hospital. Another strength of the investigation is that besides adults, it also includes children with CAI. Furthermore, mortality and length of hospital stay due to different types of CAIs was compared. We also demonstrated that infection with *C. difficile*, MECO and MKLE often leads to hospitalization for more than 6 days in a large proportion of patients. Our research also has several limitations. First, data on patients with CAI were obtained only from one hospital in Hungary; this can make it difficult to generalize our results to patients treated in other hospitals. Second, our study included only those patients with CAI who were admitted to the hospital in 2020. Third, outpatients with CAI were excluded from our investigation. Fourth, there were types of MDR bacteria which were detected only in a few cases; this can increase the uncertainty of the results related to them. Another limitation of the present study is that our results relating to hospital inpatients are only partially comparable to those in scientific literature, which often refer to the general population.

5.2 Comparison of the clinical characteristics of children with severe acute respiratory infections by cross-sectional study

Children with SARI often require treatment at intensive care units including mechanical ventilation or oxygen therapy. Furthermore, the occurrence of complications including pneumonia and thereby longer hospital stay in children with this disease have been reported to be more frequent. However, limited research exists that simultaneously investigated the factors that influence the duration of inpatient care among children with SARI due to SARS-CoV-2, influenza and RSV. Therefore, our study aimed to confirm and extend the results of previous investigations by developing a regression model incorporating the clinical data of 713 children with SARI and determining which of the patient characteristics contribute to increased length of hospitalization. Our result showed that higher proportion of patients with RSV infection required intensive care (8.94%), mechanical ventilation (8.94%), oxygen therapy (13.01%), and suffered from pneumonia (29.27%) than those with SARS-CoV-2 and influenza A infection. In addition, our findings demonstrated that the share of children below one year of age was higher among RSV infected cases (93.50%) than among those with the other respiratory infections studied. The median duration of care was also found to be the highest among children with RSV infection (median: 5 days). Our results showed that one in eight children (12.5%) in our sample had an underlying disease, the most common being asthma (17%). Considering the age distribution of children with SARI, cases with SARS-CoV-2 and RSV were significantly younger than those with influenza A. Furthermore, the duration of hospitalization was shown to be significantly longer in children with RSV infection (median: 5 days, IQR: 4–7 days) when compared to those with SARS-CoV-2 and influenza A. Using regression analysis, we have identified four factors significantly increasing the odds of hospital care longer than 4 days and these were RSV infection, pneumonia, mechanical ventilation or oxygen therapy, and underlying disease.

Our findings are in accordance with those of previous investigations. Several hospital based epidemiological studies from the USA, Lithuania, Italy, China and the Netherlands have shown that RSV was the most commonly detected pathogen in paediatric patients with SARI requiring treatment at intensive care unit (share of RSV positive cases: 3–36%), and mechanical ventilation or oxygen therapy (share of RSV positive cases: 2-42.7%). In addition, pneumonia was also a common complication among hospitalized children with RSV infection with a proportion varying between 16.1% (USA) and 24% (China). Furthermore, our research supports the findings of previous investigations showing that more than 2/3 of children suffering from RSV infection were under one year of age. It has been reported that infants are at higher risk of acquiring RSV infection due to their immature immune and respiratory system. Prematurity has also been linked to the severe form of respiratory disease caused by RSV. The clinical significance of RSV infection is further demonstrated by the fact that the median length of hospitalization in children with that disease has been found one day longer in all available studies when it was compared to that of SARS-CoV-2 and influenza. This is in line with our own result. Although the proportion of underlying diseases is not known in the general Hungarian children population, studies on comorbidities among children in France and Germany reported a prevalence of 4% and 3-3.8%, respectively. Assuming a similar disease prevalence in Hungary, it is possible that the frequency of underlying diseases is 3 or 4 times higher among hospitalized children with SARI (12.5%) than in their healthy counterparts. However, further studies are needed to support this hypothesis. Furthermore, we have found that the proportion of children with underlying diseases was the highest among those with SARS-CoV-2 (15.02%). This is in accordance with the results of previous investigations showing that the presence of comorbidities, especially asthma, increase the risk of hospitalization in children infected with the novel coronavirus. However, it is important to note that the effect of asthma in children with SARI due to SARS-CoV-2 infection on the risk of hospitalization has not been confirmed by a previous Australian study.

Prolonged hospital stay has been shown to increase the risk of nosocomial infections and the cost of treatment. However, only a few studies carried out regression analysis to identify factors influencing the duration of care in children with SARI. Of the research available, a recent investigation from Germany reported that children with RSV infections had significantly higher odds of hospitalization longer than 5 days when they were preterm born (OR: 3.37 [95% CI: 1.22–9.27]), required oxygen supplementation (OR: 5.09 [95% CI: 2.72–9.54]) and suffered from pneumonia (OR: 2.33 [95% CI:1.30–4.15]). Another study showed that children infected with RSV had significantly increased risk (relative risk: 1.40 [95%: 1.12–1.76) for treatment longer than 4 days using patients with SARS-CoV-2 infection as reference. Although previous studies have separately examined the effects of the type of respiratory infection, mechanical ventilation/oxygen therapy, pneumonia and certain comorbidities on the length of hospitalization in paediatric patients with SARS-CoV-2, influenza and RSV, these factors have not been studied in the same multiple logistic regression model. Besides providing further evidence on factors leading to prolonged hospital stay, our study goes beyond the existing research by comprehensively analysing patient characteristics influencing the duration of care. The strengths and limitations of this study should also be taken into account. Our study is the first that compared data on paediatric patients with SARI due to common respiratory viruses in a Hungarian university hospital. In addition, our research compared the duration of hospitalization in children infected with SARS-CoV-2, influenza and RSV. We extended the results of previous studies using multiple regression to identify independent factors that can increase the duration of care in children with SARI. Limitations of our research should also be considered. Data on patients with SARI were collected only from one hospital in Hungary, thus limiting our ability to generalize our findings to children treated in other healthcare facilities. Second, our investigation was limited to cases detected in one season between the 40th week of 2021 and the 20th week of 2022. In addition, it was not possible to take into consideration differences in clinical phenotypes relating to seasonal genetic changes in pathogens. A further limitation of the present investigation is that the standard definition of SARI was used to identify patients. However, this criteria may not capture children with severe RSV infection who may not present with fever. Last, we were not able to examine the effects of each underlying disease on the length of hospital stay separately.

6 SUMMARY

Community-acquired infections (CAIs), which are introduced to healthcare facilities from the area they serve, are of great public health importance. These infections can result in prolonged hospital stays for patients and can be fatal due to complications. The main types of CAIs include enteric and respiratory tract infections and infections caused by multidrug-resistant (MDR) bacteria. Of the community-acquired respiratory tract infections, severe acute respiratory infections (SARIs) are of the greatest clinical importance. Patients with SARI, especially children, often require intensive care, mechanical ventilation or oxygen therapy. In addition, children with these infections may develop complications that may result in prolonged hospitalization. However, only a limited number of studies are available in the scientific literature on the epidemiology of CAIs and SARIs. Consequently, one of the aims of our research was to collect data on the characteristics of patients with CAIs and SARIs treated in a Hungarian university hospital and to perform descriptive statistical analysis. We also aimed to investigate the duration of hospitalization among patients diagnosed with CAI and SARI due to different pathogens. Another objective of our study was to identify factors that can influence the length of hospitalization in patients with CAI and SARI.

Our study collected data on inpatients with CAIs caused by enteric pathogens, influenza viruses and MDR bacteria at the University of Debrecen Clinical Centre Nagyerdei Campus (UDCC NC) in 2020. In addition, data on children with SARI due to coronavirus, influenza and respiratory syncytial virus (RSV) were collected between the 40th week of 2021 to the 20th week of 2022. All data were obtained from information systems used at UDCC NC and recorded in a Microsoft Excel database. Subsequent to the collection of data, descriptive statistical analyses were performed, and the median number of days of care and the corresponding interquartile range were calculated for each disease. The analyses were performed using Chi-square test, Fischer exact test and Kruskal-Wallis test. Factors influencing the duration of hospital stay were identified using logistic regression analysis. Statistical analyses were performed using SPSS software package, and the results of the analyses were considered significant when p value was less than 0.05.

By analysing the characteristics of patients with CAIs, it has been determined that CAIs caused by MDR bacteria are of the greatest clinical importance in terms of in-hospital mortality and the duration of care. Furthermore, CAI related deaths due to MDR bacteria were more common in the older age group. The results of our regression analysis have shown that female sex and

hospitalization in a paediatric ward significantly decreased, whereas infections due to *Clostridioides difficile*, MDR *Escherichia coli* and MDR *Klebsiella* species, and hospitalization in a pulmonary and surgical ward significantly increased the odds of being hospitalized for more than 6 days. By analysing the clinical characteristics of children with SARI, we have shown that RSV had the greatest clinical relevance. A higher proportion of patients with RSV infection required intensive care and had longer hospitalization compared to children with SARI due to other viruses. The results of our regression model indicated that RSV infection, pneumonia, mechanical ventilation or oxygen therapy, and underlying medical conditions significantly increase the odds of a hospital stay longer than 4 days.

Our findings provide new information on patients with CAI and children with SARI, contributing to the better understanding of the epidemiology of these infections. Together with the evidence from previous studies, our results can contribute to the development hospital antibiotic stewardship and community-based programs degreasing the public health burden of infections acquired in the community. Our research can support the development of hospital-level SARI surveillance systems. The findings described also draw attention to children below 1 year of age with RSV infection, who should be payed particular attention by paediatricians during epidemic seasons. This study can provide evidence for health policy makers to allocate additional resources to hospitals, so they can cope with the increased burden of care during SARI epidemics.

However, further studies are needed to determine which factors increase the length of hospital stay and the risk of mortality for patients, particularly in the case of infections caused by MDR bacteria and in children with SARI.

7 NEW FINDINGS

Our study of CAI due to enteric pathogens, influenza viruses and MDR bacteria has shown that these pathogens are common causes of CAIs leading to hospitalization and mortality.

Our main findings:

1. Infection with *C. difficile,* MECO and MKLE has resulted in the hospitalization of a large proportion of patients with CAIs for more than 6 days.
2. Considering in-hospital mortality and the duration of care, CAIs caused by MDR bacteria have been found to be of the greatest clinical importance. In this category CAI related deaths due to MDR bacteria were more common in the older age group.
3. The results of our regression analysis have suggested that female sex and hospitalization in a paediatric ward significantly decreased, whereas CDI, MECO and MKLE infection, and hospitalization in a pulmonary and surgical ward significantly increased the odds of being hospitalized for more than 6 days.

In our study on the clinical characteristics of children with SARI, we have confirmed that SARS-CoV-2, influenza viruses and RSV are the most commonly identified pathogens in children with SARI.

Our main findings:

1. Of the viruses causing SARI in children, RSV had the greatest clinical relevance in our study.
2. By comparing the age distribution of children with SARI, we have shown that cases with SARS-CoV-2 and RSV were significantly younger than those with influenza A infection.
3. A higher proportion of patients with RSV infection required intensive care and had longer hospitalization compared to children with SARI due to other viruses.
4. The results of our regression model suggest that RSV infection, pneumonia, mechanical ventilation or oxygen therapy, and underlying medical conditions significantly increase the odds of a hospital stay longer than 4 days.

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9 LIST OF PUBLICATIONS RELATED TO THE DISSERTATION AND OTHER PUBLICATIONS

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Subject: PhD Publication List

Candidate: Nikolett Orosz
Doctoral School: Doctoral School of Health Sciences
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List of publications related to the dissertation

1. **Orosz, N.**, Gömöri, G., Ulambayar, B., Nagy, A. C.: Hospital-based cross-sectional study on the clinical characteristics of children with severe acute respiratory infections in Hungary.
   BMC Infect. Dis. 24 (1), 1-11, 2024.
   DOI: http://dx.doi.org/10.1186/s12879-024-10186-6
   IF: 3.4 (2023)
2. **Orosz, N.**, Tóthné Tóth, T., Vargáné Gyuró, G., Nábrádi, T. Z., Hegedüsné Sorosi, K., Nagy, Z., Rigó, É., Kaposi, Á., Gömöri, G., Santoso, C. M. A., Nagy, A. C.: Comparison of Length of Hospital Stay for Community-Acquired Infections Due to Enteric Pathogens, Influenza Viruses and Multidrug-Resistant Bacteria: a Cross-Sectional Study in Hungary.
   Int. J. Environ. Res. Public Health. 19 (23), 1-16, 2022.
   DOI: http://dx.doi.org/10.3390/ijerph192315935
   IF: 4.614 (2021)*

List of other publications

3. Kaposi, Á., **Orosz, N.**, Nagy, A., Gömöri, G., Kocsis, D.: A comprehensive study on the factors influencing the generation of infectious healthcare waste in inpatient healthcare institutions in Hungary.
   J Air Waste Manage. 74 (11), 828-841, 2024.
   DOI: http://dx.doi.org/10.1080/10962247.2024.2408011
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* In the year of acceptance (2021) the journal has impact factor: 4,614.

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4. Fazekas-Pongor, V., Fehér, Á., Major, D., Szarvas, Z., Árva, D., Dósa, N., Pártos, K., Péterfi, A., Fekete, M., Mészáros, Á., **Orosz, N.**, Szendi, K., Tóth, E., Paulik, E., Ungvári, Z., Terebessy, A.: A prevenciós szakrendelés keretében ajánlott védőoltások, illetve kommunikációs stratégiák az oltással kapcsolatos félelmek kezelésére.
Népegészségügy. 101 (1), 51-56, 2024.

Total IF of journals (all publications): 10.114
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