Differences in severity of bronchiolitis among newborns and infants younger than one year of age before and after the lockdown due to COVID-19 pandemic

Sporkert, Nora Muriel

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Nora Sporkert

DIFFERENCES IN SEVERITY OF BRONCHIOLITIS AMONG NEWBORNS AND INFANTS YOUNGER THAN ONE YEAR OF AGE BEFORE AND AFTER THE LOCKDOWN DUE TO COVID-19 PANDEMIC

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Assist. Prof. Peter Dahlem, MD, PhD

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With this scientific work, my studies in human medicine are now finally over.
I would like to thank Assist. Prof. Peter Dahlem, MD, PhD, for the opportunity to write my thesis in the Department of Pediatrics and for the supervision during this research.
Furthermore, a huge thank you goes to my boyfriend Luca and my good friend Katha as well as to my family, who motivated, cheered me up and looked after me so wonderfully during this period which was not always the easiest one.
I look back on a great time in which I was able to learn a lot. But now, I am looking forward to work as a doctor soon.

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LIST OF ABBREVIATIONS

AdV – Adenovirus

CCT – computed chest tomography

COVID-19 – coronavirus disease 2019

CI – confidence interval

CPAP – continuous positive airway pressure

Flu A – Influenza A virus

hMPV – Human metapneumovirus

hRV – Human rhinovirus

hRV/EV – Human rhinovirus/enterovirus

ICU – intensive care unit

NPIs – non-pharmaceutical interventions

OR – odds ratio

PCR – polymerase chain reaction

PIV 3 – Parainfluenza virus 3

RSV – Respiratory syncytial virus

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus type 2

SPSS – Statistical Package for the Social Science

1. INTRODUCTION

1.1 Bronchiolitis

1.1.1 Definition

Bronchiolitis is defined as an inflammatory disease of the lower respiratory tract (distal bronchioles) in infancy and early childhood caused by a viral infection (1-3). This disease is based on a clinical diagnosis characterized by swelling of the small airways and resulting in obstructive symptoms (2-4).

Up to now, there is no international standard definition of bronchiolitis in infancy (5). This study will focus on European definitions as stated in (5):

> *“[...] Bronchiolitis in children less than 12 months of age and restrict[ed] to the first presentation only [...]”*

1.1.2 Epidemiology

Bronchiolitis is the most common cause of acute lower respiratory tract infections in infancy (1). The prevalence ranges from 18-32 % in the first twelve months of life (6). At the age of three to six months, the incidence of this disease is at its highest (1,7). Bronchiolitis is also the most common reason for admission to the hospital with a hospitalization rate of 2-3 % (1,2). The highest hospitalization rate of Respiratory syncytial virus (RSV)-induced bronchiolitis during infancy appears within 30-90 days after birth as the level of transplacental acquired maternal immunoglobulin decreases (8).

In Germany, infants less than one year of age develop bronchiolitis predominantly during the winter months, characteristically from October to April. For bronchiolitis caused by RSV the peak of disease cases occurs in January and February, for other causes this period can differ. E.g. Human rhinovirus (hRV)-induced bronchiolitis usually presents mainly during fall or spring (1,9).

1.1.3 Etiology

The frequency of certain viruses that can cause bronchiolitis during infancy changes depending on the age of the children, visualized in Figure 1. The most common viral causative agent of bronchiolitis in infants is RSV (4). This virus belongs to the Pneumovirus genus in the family of Paramyxoviridae with two subtypes (A and B) along with multiple genotypes and serotypes. Between 50-80 % (6) of all bronchiolitis in children younger than one year of age who are hospitalized are caused by RSV (3,6,10). The second most common pathogen detected in nasopharyngeal swabs is hRV (1). Less common respiratory organisms include Human metapneumovirus (hMPV), Parainfluenza virus 1-3 (PIV 1-3), Adenovirus (AdV), Coronavirus (CoV), Influenza virus A and B (Flu A and B), Enterovirus (EV) and Human bocavirus (hBoV) (2,3,8).

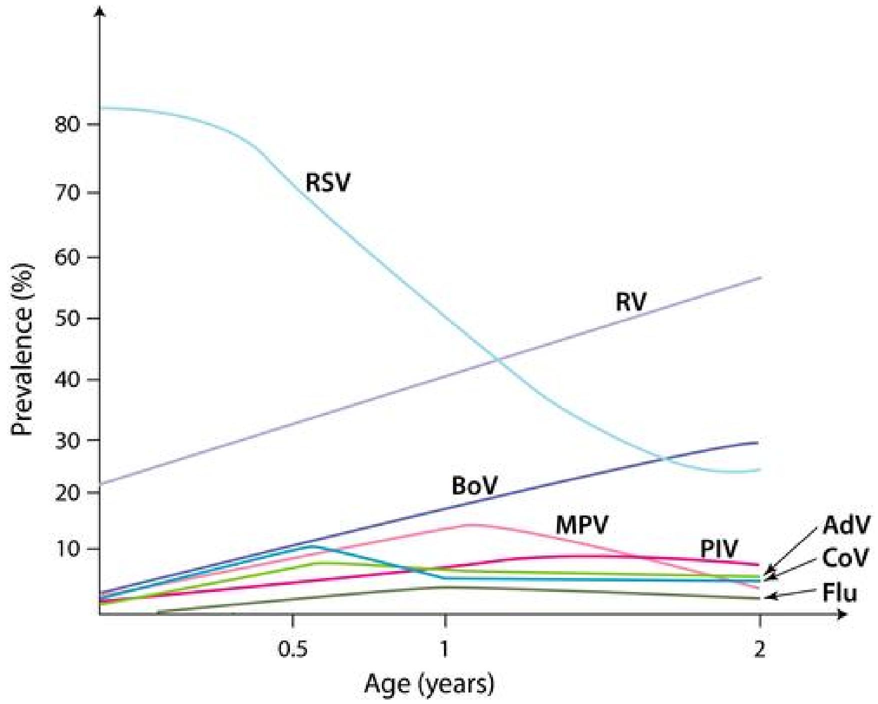

Figure 1. Frequency of different viruses causing bronchiolitis during infancy (6) RSV-Respiratory syncytial virus, RV-Rhinovirus, BoV-Bocavirus, MPV-Metapneumovirus, PIV-Parainfluenza virus, AdV-Adenovirus, CoV-Coronavirus, Flu-Influenza virus

All of the aforementioned pathogens are not necessarily always present alone but can also be responsible for bronchiolitis as a coinfection. Depending on the study, multiple infectious agents are detected in 6-30 % (8) of bronchiolitis. The most common coinfection includes RSV and hRV. In exceptional cases, bacterial superinfections can be verified, but these are rarities (1,3,8).

The viral lower respiratory tract infection spreads through nasal and/or conjunctival mucosal inoculation with contaminated exudates. Dissemination can likewise be accomplished by inhalation of large virus-containing respiratory droplets at a distance of less than two meters from the infected infant. The main pathway of infection occurs via hands. RSV as the primary pathogen can be detected on the respiratory epithelium for up to seven to ten days. It is able to survive persistently in secretions, on clothing and gloves for several hours and on the skin for over 30 minutes. The incubation period lasts four to six days (3,8).

The risk of developing bronchiolitis and its severity can be influenced by several factors during infancy (6,8). The most important and crucial risk factors for severe disease include (8,11,12):

- hemodynamically important congenital heart disease
- chronic lung disease of prematurity (bronchopulmonary dysplasia)
- neuromuscular impairment
- prematurity
- immunodeficiency and immunosuppression
- chromosomal aberrations

Breastfeeding is the only known factor that protects newborns and infants against severe bronchiolitis (2,13).

1.1.4 Pathophysiology

The pathophysiology of bronchiolitis is described in Figure 2. It is driven by two pathways. First, it is associated with direct cellular damage by viral replication caused by cytopathic effects of the pathogens. Second, the disease is based on exaggerated local and systemic immune reactions. These immune responses are individually variable and therefore can influence the severity of the respiratory infection (1,8).

The underlying process of bronchiolitis begins with necrosis of respiratory epithelial cells, severe destruction of cilia and peri-bronchial infiltrate of lymphocytes and neutrophils in terminal and respiratory bronchioles. The following inflammatory reaction leads to submucosal edema in the airways and surrounding tissues as well as increased production of secretions. In addition, accumulation of exfoliated epithelial cells, cellular debris, inflammatory cells, and fibrin occurs which result in intraluminal obstruction. This can progress to either partial airway narrowing in various lung segments and lobes by valve mechanism that consequently terminates in hyperinflation. Clinical sign of valve mechanism typically includes an end-inspiratory crackling sound. Alternatively, atelectasis can develop in lungs due to complete airway obstruction caused by lack of ventilation. Subsequently, ventilation-perfusion mismatch can be expected culminating in hypoxemia, rising carbon dioxide parameters, and right-to-left shunt. Due to impaired lung function (hyperinflation) or defective lung function (atelectasis), elevated work of breathing and impaired respiratory muscle function are seen. Characteristic features include low-lying diaphragm, palpable spleen and liver, and horizontal rib pattern with unfavorable attachment of inspiratory intercostal muscles. In severe cases of bronchiolitis, respiratory fatigue is often observed. The underlying reason for this is the increased respiratory resistance and reduced dynamic lung compliance (1-3).

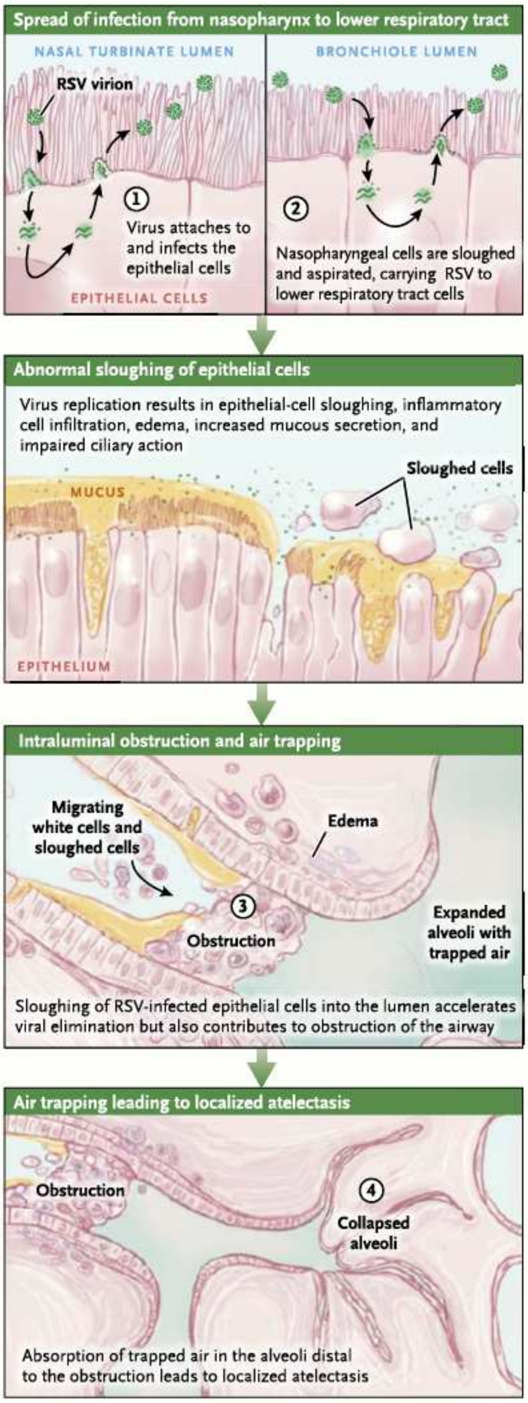

Figure 2. Pathophysiology of RSV-bronchiolitis (8)

The course of bronchiolitis is self-limiting (14). The epithelial cells initiate their regeneration three to four days after the symptoms have disappeared (8).

1.1.5 Symptoms

Infants with bronchiolitis go through two characteristic stages. In the prodromal stage, which occurs before the clinical presentation of bronchiolitis, infants show symptoms of upper respiratory tract infection (4,6). To this belongs rhinitis, rhinorrhea, nasal obstruction, dry and irritable cough, as well as fever below 39 degrees. However, febrile temperatures occur in only 30 % (1) of all infants younger than one year of age (1,3,4,9).

After one to three days, the second stage occurs, which is associated with the clinical picture of bronchiolitis (infection of the lower respiratory tract) (1). Infants suffer from persistent cough, fever below 39 degrees and signs of dyspnea caused by obstruction of small airways (7,14). Complaints of breathlessness include tachypnea, nasal winging, cyanosis, pulmonary hyperinflation, intercostal/subcostal/supraclavicular retractions due to difficulty in work of breathing, use of respiratory accessory and abdominal muscles, grunting, and nasal bleeding (1,3,4,6,9). There can also be restriction of feeding as well as weakness in drinking, resulting in dehydration and metabolic acidosis in the infant, depending on the severity of bronchiolitis (1,2,7). Premature babies and infants younger than three months of age often have central apnea combined with bradycardia. These episodes of apnea often present as the only and earliest symptom of bronchiolitis, which is most frequently induced by RSV. This phenomenon is caused by direct disruption of the respiratory center by the virus. In severe cases of bronchiolitis, respiratory insufficiency can develop. This incompetence is expressed by signs of fatigue, recurrent respiratory failure, and lack of adequate oxygen saturation despite appropriate oxygen administration. Intensive care and respiratory support are mandatory (1,3,7). On clinical examination, end-inspiratory crackles and/or wheezing can usually be auscultated. In some cases, an expiratory whistle may also be heard (3,9). All of the above-mentioned symptomatology is summarized in Figure 3.

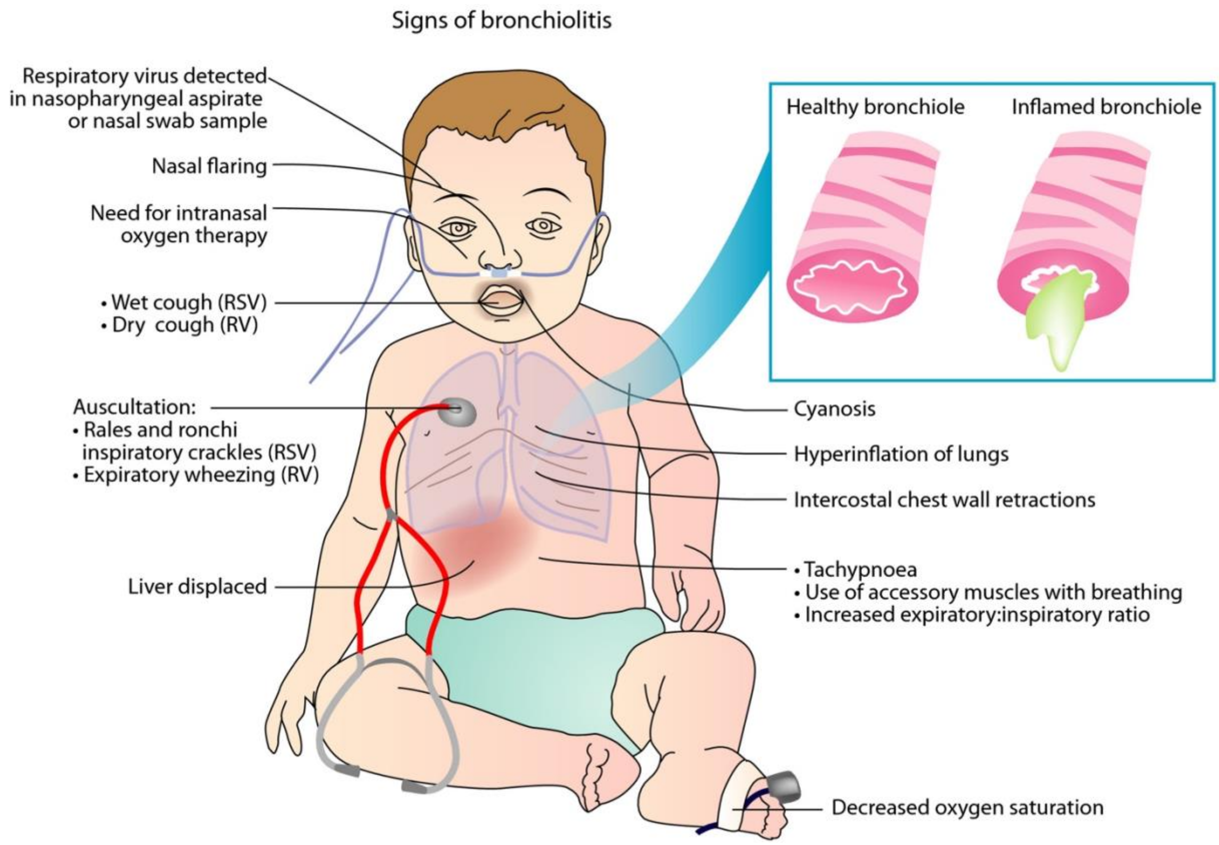

Figure 3. Symptoms of bronchiolitis (6)

Bacterial superinfections can be encountered in infants with bronchiolitis, but they are very rare (less than 1 %) (15,16). Typical signs are persistent high fever, deterioration of general condition, and clinical picture of sepsis (2,3). Children with bronchiolitis have a 29-59 % higher risk of suffering from hyponatremia as a complication of the lower respiratory tract infection. The presence of the aforementioned electrolyte imbalance may negatively affect the severity of bronchiolitis (17-19).

The above-described symptomatology of bronchiolitis can fluctuate minute by minute. This dynamic occurs predominantly at the beginning of the disease. The underlying cause is related to coughing up of mucus and debris situated in the small airways as well as the change from sleep to restlessness of infants (1,2,9).

The course of bronchiolitis during infancy varies from individual to individual. Symptoms are at their strongest from the third to the fifth day of the disease. In most cases, the clinical picture improves after two to three weeks, depending on the hydration of the infant. Residual signs, primarily cough, persist in 10-20 % (9) of infants after three weeks (1,9,14).

Most infants experience a mild form of bronchiolitis that can be treated as an outpatient at home (6).

Acute bronchiolitis in infants less than one year of age is typically the first manifestation of obstructive airway disease experienced during their early life. Infants who have suffered from one or more bronchiolitis during infancy are at greater risk for recurrent obstructive bronchiolitis or asthma later in life (3).

1.1.6 Diagnostics

The diagnosis of bronchiolitis is mainly anchored on patient's history and clinical assessment. Determination of respiratory rate measured per minute and pulse oximetry for the evaluation of oxygen saturation are recommended in every patient. Any further investigations are not routinely recommended for infants by guidelines (1,7,9).

Laboratory tests

A swab of nasopharyngeal secretion can be collected using polymerase chain reaction (PCR) or rapid test to identify viruses in the respiratory tract. However, this is only used to determine if isolation of the patient is necessary (for example in the case of RSV-infection). Virus testing is generally not recommended by guidelines since the result has no significance for the outcome of the disease and no therapeutic consequences. A complete blood count is indicated only in infants younger than the age of one or two months to rule out differential diagnosis of fever. Blood gas analysis and electrolyte monitoring are appropriate only in serious cases like severe respiratory failure or distress to assess the respiratory and metabolic status of the patient. Blood cultures are taken only in cases of suspected sepsis as well as severe disease due to the rarity of bacteremia. Urinalysis and urine culture should be completed only in infants less than two months of age with fever exceeding 38 degrees, in older infants with known risk factors for urinary tract infection and in case of clinical uncertainty. Equally, these tests are indicated when no other source of infection is present, or body temperature continues to rise. However, these procedures are not recommended as a routine examination in infants with acute bronchiolitis. Indeed, acute bronchiolitis and urinary tract infection occur concomitantly in only 1-7 % (9) of infants (1,3,9).

Imaging

Lung ultrasound can be performed to detect cardiopulmonary disease as well as to diagnose bronchiolitis. Ultrasound is more specific than radiography, and the findings correlate very well and better with patient's clinical condition. However, the importance of this non-invasive procedure in making diagnosis and in assessing severity of the disease has not been well established (1,9). A chest x-ray is only ordered if complications are suspected (pneumothorax, bacterial superinfection), pneumonia must be excluded, and patient has a severe, atypical course. This includes fever above 39 degrees and focal crackles on auscultation (1,14). Most infants have a normal radiograph with no pathologic findings that are characteristics of acute bronchiolitis (9). The typical features of acute bronchiolitis on X-ray include (1,3,9):

- discrete peri-bronchial or parenchymatous infiltrates
- hyperinflation areas on both sides
- atelectasis, predominantly in the right upper lobe

Routinely applied X-rays result in unnecessary antibiotic administration which can lead to resistance in patients (1,9,20). The underlying reason for the increased ordering is that atelectasis are difficult to separate from infiltrates (3).

The history and clinical examination of the patient are not only essential for the diagnosis but are equally helpful in assessing the severity of acute bronchiolitis. This lower respiratory tract disease can be divided into three degrees of severity depending on respiratory rate, oxygen saturation, thoracic retractions, and current nutritional situation as can be seen in Table 1. The assessment of severity may be complicated by the dynamic course of symptoms of bronchiolitis (1-3).

Table 1. Degrees of severity of bronchiolitis (3)

findings	mild	moderate	heavy
respiratory rate	< 40 /min	40-70 /min	> 70 /min
O2-saturation (under room air)	> 92 %	88-92 %	< 88 %
retractions (sternal/thoracic)	absent	+	++
nutrition	unproblematic	difficult	impossible

The classification of bronchiolitis into degrees of severity facilitates the decision whether outpatient or inpatient treatment is necessary (4). For moderate and severe bronchiolitis, infants must be hospitalized (3). Factors to be considered are (3,7):

- early signs of respiratory failure (respiratory rate greater than 60 /min, central cyanosis, grunting, chest wall retractions)
- underlying diseases leading to impaired respiratory capacity (cystic fibrosis, bronchopulmonary disease, congenital hereditary defects)
- serious discomfort of the infant
- inadequate oxygen saturation (below 92 % despite oxygen administration), increasing restlessness
- inability to drink or signs of dehydration (decreased urinary output, weight loss)
- difficult social circumstances
- apneas

1.1.7 Differential diagnosis

Before diagnosing acute bronchiolitis, various infectious and non-infectious diseases should be considered (1,3,9,14,21):

- obstructive bronchitis
- bacterial infections of the respiratory tract (pneumonia)

- pertussis
- other causes of upper respiratory tract symptoms
- asthma
- croup
- gastroesophageal reflux disease (GERD)
- foreign body aspiration

1.1.8 Therapy

Most of all infants suffering from acute bronchiolitis are treated as outpatients. Only 2-3 % of sick infants require hospitalization (3,22). There is currently no treatment available for acute bronchiolitis that reduces the course of disease or accelerates resolution of symptoms (8). The most important therapeutic approach is based on supportive measures. Emphasis is placed on minimal handling including avoidance of unnecessary examinations, manipulations, and stress, ensuring adequate hydration as well as proper oxygenation (1,3,23).

Fluids can be given either via trans-nasal/oral gastric tube or replaced through intravenous liquid substitution to keep the infant adequately hydrated. For substitution, an isotonic solution is preferred over a hypotonic one to minimize the risk of hyponatremia. A satisfying oxygenation can be achieved by means of oxygen supplementation or respiratory support (for example nasal high-flow therapy). The cutoff for lower oxygen saturation ranges from 90 to 92 % (1) depending on the guidelines. Continuous positive airway pressure (CPAP) or invasive ventilation can be used if the condition is severe (1,3).

In addition to these essential basic interventions, superficial nasal suctioning can be performed as well as decongestant nasal drops can be administered to improve child's work of breathing and to facilitate feeding. Infants are obligate nasal breathers and thus benefit from free nasal airways. Respiratory physiotherapy may be ordered but is not routinely recommended by guidelines due to lack of scientific evidence (1,3,9).

Drug therapy is generally not supported except in conditions with impeding respiratory insufficiency or known preexisting hyperactivity of the bronchial system (bronchopulmonary disease, recurrent bronchiolitis). Usable pharmaceuticals including bronchodilators (epinephrine, adrenalin, salbutamol), corticosteroids, leukotriene receptor antagonists (montelukast), and antibiotics should be routinely avoided in the treatment of acute bronchiolitis. Bronchodilators should be generally excluded due to their side effects (tachycardia, tremor, decline of oxygen saturation), increasing cost, and minimal clinical benefit (short-term, transient improvement in symptoms). They do not affect oxygen saturation or duration of hospitalization in a beneficial way. Inhaled use of epinephrine also does not ameliorate any clinical outcome. For leukotriene receptor antagonists, the definitive conclusion of the corresponding effect on the duration of hospitalization as well as the severity of the disease is equally unavailable. Antibiotics should only be given in cases of confirmed and urgent suspicion as well as in proof of bacterial infection. They are likewise indicated for respiratory failure with indication for intubation or mechanical ventilation. Secondary bacterial infections are very rare. The risk of sepsis or meningitis in infants with acute bronchiolitis is less than one percent. Otitis media occurs in 60 % (9) of ill children. Unnecessary antibiotic administration leads to adverse effects for the young patient and development of resistance to antibiotics (1,3,8,9).

Scientific results regarding the administration of inhaled hypertonic saline three percent are contradictory. It is not recommended by Australian and UK guidelines (1,9). Figure 4 summarizes the therapeutic strategy for bronchiolitis based on the latest scientific evidence.

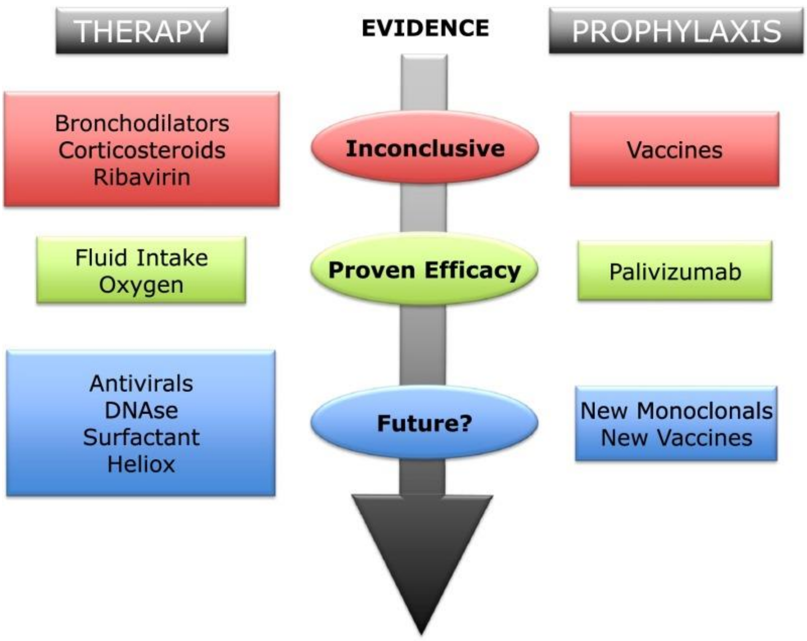

Figure 4. Therapeutic regime of bronchiolitis based on latest evidence (24)

1.1.9 Prognosis

Acute bronchiolitis is a respiratory disease with a self-limiting course and good prognosis (14,25). It heals completely in almost all cases. The mortality rate in young children is between 1-2 % (26), which is extremely low. Infants with cardiopulmonary or immunologic pre-existing disorders are most affected (1,26).

After the disease, infants may still manifest a hyperreactive bronchial system (3). Connected with this condition is the increased risk of recurrent obstructive bronchiolitis as well as asthma (9,26). Patients who have undergone a severe course of bronchiolitis (most commonly caused by RSV or hRV) show an increased risk of developing asthma later in life (8).

1.1.10 Prevention

Currently, there is no curative therapy for viral bronchiolitis in infants that can shorten the course of bronchiolitis and accelerate the remission of symptoms (8).

As mentioned at the beginning, RSV is the most common viral agent of acute bronchiolitis in infancy (4). For this reason, this chapter will focus primarily on the prophylaxis of RSV bronchiolitis.

The S2k guideline "Guideline for the prophylaxis of severe respiratory syncytial virus (RSV) diseases in high-risk infants" recommends general preventive measures in the case of viral bronchiolitis. Among them are regular hand hygiene by contact persons, avoidance of tobacco smoke exposure in the proximity of the infant, breastfeeding of the infant, and abstinence of large crowds such as nursery (predominantly in high-risk infants). High-risk infants are those who have an increased risk of suffering a severe course of bronchiolitis due to their pre-existing condition. As such, they typically encompass infants with prematurity, hemodynamically relevant congenital heart disease in infants, chronic lung disease, neuromuscular disease, immunodeficiencies, and chromosomal aberrations (13,27,28).

According to the guidelines, RSV prophylaxis with Palivizumab, a monoclonal antibody, is currently only recommended for children at risk (24,28). In this passive immunization, the infant receives an intramuscular injection once monthly for a total consecutive period of five months during the RSV season (1). The goal is to protect the patient at increased risk from severe RSV bronchiolitis. In accordance with other studies, monthly administration can reduce hospitalization rates up to 50 % (28,29). The most recent information suggests that RSV prophylaxis is only advised for certain indications due to limited clinical usage and immense financial costs. Those involve young infants with prematurity (less than 29 weeks of gestation), chronic lung disease in premature infants (bronchopulmonary dysplasia), and hemodynamically congenital heart disease (cyanotic and acyanotic) during the first and less frequently during second year of age (24,26,28,30). Active immunization does not presently exist, but is on the way. A vaccine against RSV has recently been approved for people over 60 years of age (31,32). At the moment, healthy infants are not entitled to RSV prophylaxis (28). A new passive immunization with Nirsevimab (monoclonal antibody), which only needs to be injected once at the beginning of the RSV season, should be available for term infants at the end of December for the winter season 23/24 of RSV (33,34).

1.2 Influence of covid-19 pandemic on bronchiolitis in newborns and infants

Covid-19 pandemic has been a global health and social problem since March 2020 (35). Covid-19 infection is a contagious viral respiratory infection caused by SARS-CoV-2 (36). The prevalence in the pediatric population is very low (2-5 %). Transmission of SARS-CoV-2 occurs primarily from person-to-person via droplets or aerosols produced by breathing, talking, sneezing, or coughing (37). The clinical course of covid-19 infection in children is usually manifested as non-symptomatic (15 %), mild (40 %) or moderate (40 %) compared to adults (38). The infection begins with an upper respiratory tract disease. The most common clinical complaints are fever (51.6 %) and cough (47.3 %) (39). Treatment of children with covid-19 infection is primarily based on a supportive care strategy focused on appropriate levels of oxygenation and satisfied nutritional status (40).

To stop human-to-human transmission of the virus, special measures were implemented like going out restrictions ("lockdown") and avoiding contact. The most effective measure is the introduction of non-pharmaceutical interventions (NPIs) including hand hygiene and wearing of masks. These NPIs positively affect the transmission rate of SARS-CoV-2 and lead equally to a reduction of other respiratory infections, especially RSV infections. Unfortunately, these measures like daycare and school closure as well as lockdown can also result in an overall reduction in infections during infancy and early childhood resulting in a negatively changed immune status (41,42). As a result, RSV infections have almost completely disappeared during this period (42,43). Consequently, this reveals a weak and vulnerable immune system in infants during and after the covid 19 pandemic (42,44).

One can speculate that this circumstance is reflected in the severity of bronchiolitis. Therefore, this study will analyze the disease severity of bronchiolitis in newborns and infants under one year of age before and after the lockdown.

2. OBJECTIVES

Aims of this study are:

- to analyze general information of newborn and infants with bronchiolitis younger than one year of age including
  - hospitalization rate
  - virus that causes bronchiolitis
  - number of coinfections revealed by respiratory multiplex PCR
  - month of admission
  - length of hospital stay
- to investigate sociodemographic factors of studied population including
  - age
  - sex
- to evaluate the severity of bronchiolitis before and after the lockdown in newborns and infants younger than one year of age with bronchiolitis in regard of
  - development of bacterial superinfections
  - requirement of oxygen therapy
  - need for mechanical ventilation/respiratory support
  - numbers of intensive care unit (ICU) admission

The hypothesis of this study is that the severity of bronchiolitis caused by any virus in newborns and infants is negatively affected by the lockdown of the covid-19 pandemic.

3. MATERIALS AND METHODS

3.1 Ethical approval

The Plan of Research was approved by the Institutional Review Board of the Medical School Regiomed Coburg on February 27th, 2023.

3.2 Study design

This scientific thesis is a retrospective study that analyses patient records (including information of the disease history of each individual patient) of newborns and infants younger than one year of age with bronchiolitis. However, as the study focuses on the severity of bronchiolitis, all analysis except chapter hospitalization rate of bronchiolitis used only the data of newborns and infants younger than one year of age with bronchiolitis as diagnosis of discharge.

The aim of this study is to investigate the effect of the lockdown due to covid-19 pandemic on the severity of bronchiolitis in children younger than one year. The lockdown officially began on 22nd of March, 2020, and ended in May 2021 (45-47). We used the lockdown as a guideline for the group division because it is speculated to be responsible for both life incisions and changes in the health status/evolution of diseases of the population. As the study aims to investigate the effects of resuming physical contact and social interactions after the lockdown, it was decided to form one group before the start and one group after the end of the lockdown. Accordingly, group A includes pediatric children who were hospitalized before the lockdown. Data were analyzed from 1st of April, 2018 until 31st of March, 2020. Group B compromises patients admitted to the hospital for bronchiolitis after the lockdown. We are referring to data beginning on 1st of May, 2021 and ending on 30th of April, 2023. Group A and B were subsequently compared to test our hypothesis.

The virus of bronchiolitis was detected by antigen test (SD Biosensor) or PCR (Medical Wire and Equipment (MEW)). Coinfection was proven by respiratory multiplex PCR. This test usually screens for the presence of the following pathogens in the patient's sample: Bocavirus, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, Coronavirus HKU1, Adenovirus, Rhinovirus, Human metapneumovirus, Parainfluenza virus 1-4, Respiratory syncytial virus, Influenza virus A and B, Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae. Bacterial superinfection was recorded as present when antibiotics were prescribed.

3.3 Data collection

The data about the patient and his/her medical history were collected electronically via Orbis (electronical platform of the Regiomed hospital in Coburg; Orbis®, Dedalus Healthcare, Bonn, Germany). This information was subsequently exported to Microsoft Excel 2013 (version 16.75). Finally, a statistical evaluation was performed by using IBM SPSS Statistics (version 29.0.1.0). The collected data are anonymized. It is not possible to trace individual patients of this study.

3.4 Sample

This study focused on newborns and infants aged 0-365 days who were treated in the pediatric department of the Regiomed hospital in Coburg, teaching hospital of the Medical School Regiomed, University of Split, School of Medicine, due to bronchiolitis. We observed and compared two time periods before and after the covid-19-driven lockdown.

Inclusion criteria:

- pediatric patient under the age of one year on the day of hospitalization
- bronchiolitis as diagnosis of discharge

  As an exception, in chapter hospitalization rate of bronchiolitis, all children under one year of age who presented to the pediatric emergency department with suspicion of bronchiolitis were used in the evaluation. For all other statistical analyses in the study, only children with bronchiolitis as diagnosis of discharge were included.

Exclusion criteria:

- incomplete documentation of medical records

3.5 Statistical analysis

The collected data were exported into Microsoft Excel and statistically analyzed by using Statistical Package for the Social Science (SPSS). Statistical procedures were performed according to standard statistical principles. The variability of the data was presented by using 95 % confidence interval. The descriptive presentation of the results included the minimum, maximum, median, mean and standard deviation for continuous variables, as well as absolute and relative frequencies for categorical variables. For the statistical tests, linear regression is used to model the continuous outcomes with age and sex as covariates. The main predictor is pre-lockdown versus post-lockdown. For the binary outcomes, logistic regression is performed with age and sex as covariates and lockdown (before/after) as predictor variable. In our study, the statistical significance is defined as $P < 0.05$. Chi-square test was performed to calculate the *P*-value for the association between two categorical variables. If the absolute number per cell was less than five, Fisher test was carried out for the determination of the *P*-value in order to obtain a more precise significance. To find out whether two dependent samples differ significantly (direct comparison), the Wilcoxon-Mann-Whitney test was applied.

4. RESULTS

4.1 General information of the study population

4.1.1 Hospitalization rate of bronchiolitis

The hospitalization rate of bronchiolitis in children before and after the lockdown is shown in Figure 5. Before the lockdown, 163 children were hospitalized due to presumption of bronchiolitis between April 1st, 2018 and March 31st, 2020. Bronchiolitis as diagnosis of discharge was recorded in 128 cases (78.5 %). The remaining 35 children (21.5 %) received a diagnosis of another disease. After the lockdown, 160 children presented to the pediatric emergency department with suspicion of bronchiolitis between May 1st, 2021 and April 30th, 2023. 119 pediatric patients (74.4 %) were admitted and treated for bronchiolitis as diagnosis of discharge. The other 41 children (25.6 %) were hospitalized for a different diagnosis.

No statistically significant difference was found between the rate of hospitalization of bronchiolitis before and after the lockdown (P = 0.379).

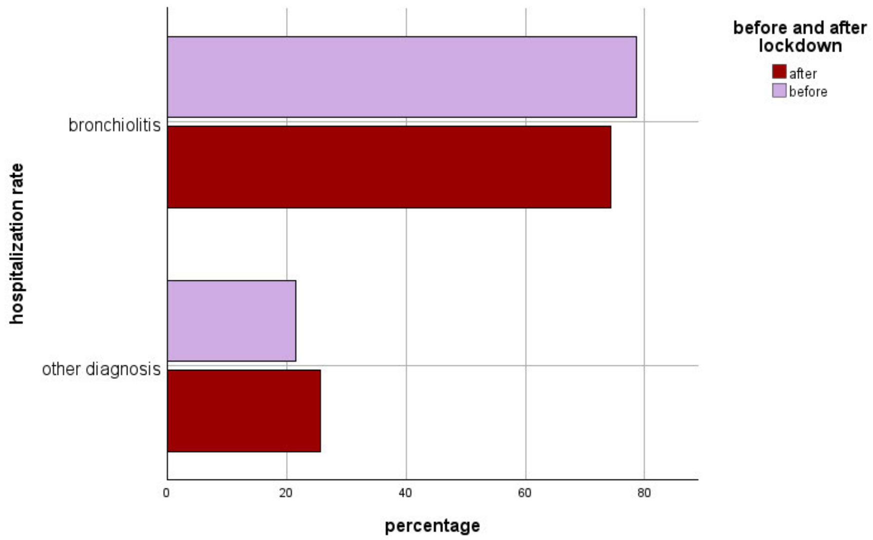

Figure 5. Hospitalization rate of bronchiolitis in children before and after the lockdown
Data are presented as percentage

4.1.2 Virus

The viral cause of bronchiolitis in children before and after the lockdown are demonstrated in Figure 6. Before the lockdown, 128 patients were hospitalized due to bronchiolitis. With 93 cases (72.7 %), RSV was the most common reported viral pathogen. hRV/EV was the second most frequent virus with five cases (3.9 %) followed by hMPV with three reports (2.3 %). Flu A was detected in only one patient (0.8 %). In 26 children (20.3 %)

no virus could be identified. After the lockdown, 119 patients were enrolled with a diagnosis of bronchiolitis. RSV was the most prevalent virus detected among 100 cases (84.0 %) followed by hRV/EV with 8 reports (3.2 %). hMPV was confirmed in only three patients (1.2 %). Flu A as well as Parainfluenza virus 3 (PIV 3) were identified in only one child (0.4 %). In 38 children (15.4 %) the cause of bronchiolitis was not of viral origin.

A statistically significant difference was found between all kind of responsible viruses before and after the lockdown with *P* = 0.021. Since the number of different viruses is very tiny, the statistical output should be taken with a certain degree of caution.

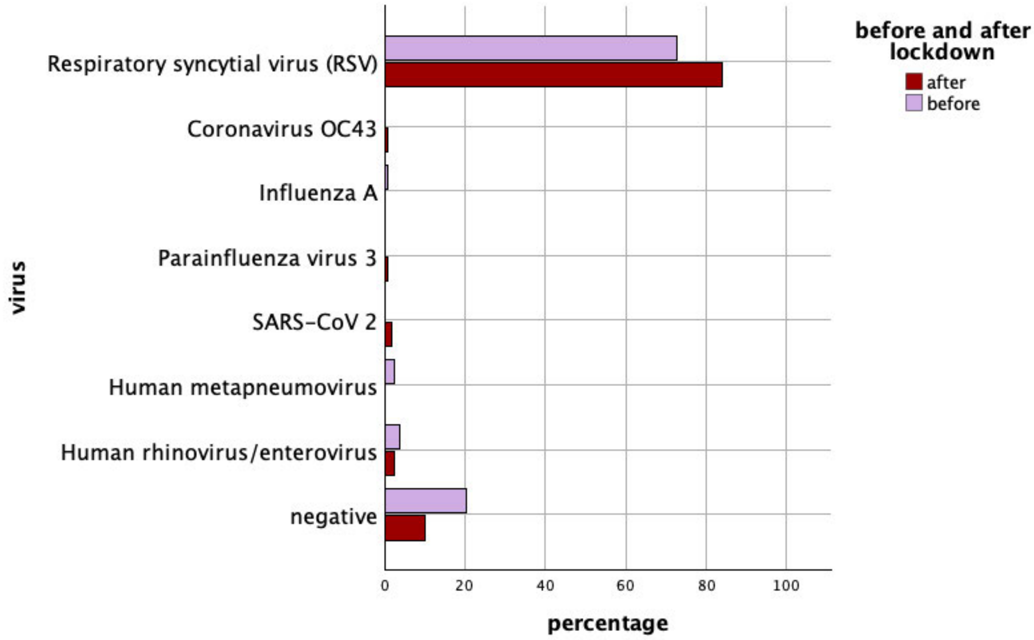

Figure 6. Virus causing bronchiolitis before and after the lockdown
Data are presented as percentage

4.1.3 Coinfection

Coinfection was detected in the study using a multiplex PCR. This test was performed in 32 (13.0 %) out of 247 children. Of these, 17 (13.3 %) tests were taken before and 15 (12.6 %) after the lockdown (*P* = 0.874). The results are presented in Table 2.

The different coinfections detected in our studied population are shown in Figure 7. Before the lockdown, coinfection consisting of RSV and Influenza A/H1-2009 was detected in two patients (1.6 %). In one case (0.8 %), RSV was observed together with Bordetella parapertussis. RSV with Moraxella catarrhalis and Streptococcus pneumoniae was likewise confirmed in one single child (0.8 %). The majority of all children examined, 124 in total

(96.9 %), presented without coinfection. After the lockdown, RSV combined with hRV/EV was detected in two children (0.8 %). In one case (0.8 %), RSV was identified together with AdV. No coinfection was observed in 116 children (97.5 %).

No statistically significant difference could be observed in children with bronchiolitis in regard of coinfection ($P = 0.169$). However, it is impossible to make a definite statement with such few cases.

Table 2. Multiplex PCR performed in patients with bronchiolitis before and after the lockdown

multiplex PCR	**before lockdown (N = 128)**	**after lockdown (N = 119)**	**total (N = 247)**	***P*[a]**
yes	17 (13.3 %)	15 (12.6 %)	32 (13.0 %)	0.874
no	111 (86.7 %)	104 (87.4 %)	215 (87.0%)	

[a] chi-square test: $P < 0.05$ would be considered statistically significant

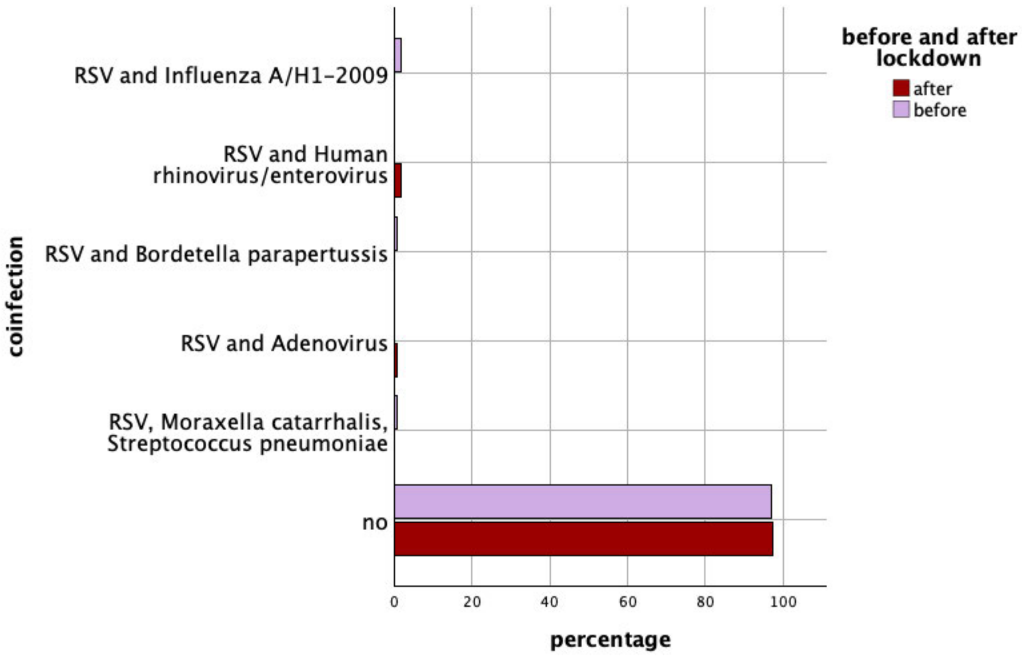

Figure 7. Coinfection in patients with bronchiolitis before and after lockdown
Data are presented as percentage

4.1.4 Month of admission

The different month of admission due to bronchiolitis before and after the lockdown is presented in Figure 8. Before the lockdown, children were most frequently hospitalized for bronchiolitis in January (27 / 21.1 %), February (51 / 39.8 %), and March (20 / 15.6 %). A minority of seven children (5.5 %) were hospitalized in April and six children (7.0 %) in May. There was only one hospitalized child (0.8 %) in June. Two young patients (1.6 %) each attended the hospital in September and October for inpatient treatment of bronchiolitis. A total of nine patients (7.0 %) were hospitalized in December. No children were admitted as inpatients for bronchiolitis in July, August, and September. After the lockdown resolution, children with bronchiolitis presented to the hospital predominantly during fall and winter months namely October (26 / 21.8 %), November (46 / 38.7 %), and December (23 / 19.3 %). Five children (4.2 %) were hospitalized in January, two children (1.7 %) in February, four children (3.4 %) in March, and one child (0.8 %) in April. There were five admissions to the hospital in July (5.0 %), a single one in August (0.8 %), and six in September (5.0 %). No cases of hospitalization for bronchiolitis were documented in May and June.

A statistically significant difference in the month of admission before and after the lockdown could be proven ($P < 0.001$).

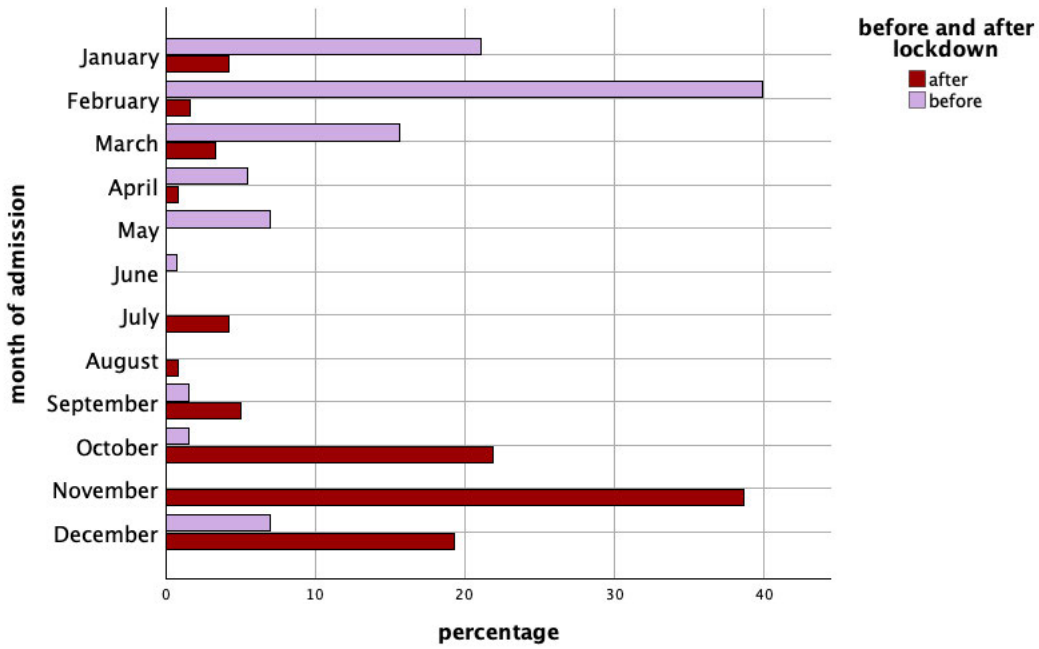

Figure 8. Month of admission due to bronchiolitis before and after the lockdown
Data are presented as percentage

4.1.5 Length of hospital stay

All data regarding length of stay in the hospital in patients with bronchiolitis before and after the lockdown can be seen in Figure 9. Before the lockdown, the length of hospital stay varied from one to twelve days. However, no child was hospitalized for ten days. Most children were hospitalized for two days (38 / 29.7 %) closely followed by three (22 / 17.2 %) and four days (23 / 18.0 %). Six children (4.7 %) spent one day as inpatients, twelve (9.4 %) five or six days, six (4.7 %) seven days, three (2.3 %) eight days, two (1.6 %) nine, ten or eleven days. Considering the time after the lockdown, children were hospitalized between one and 15 days. No child was admitted to the hospital for 13 or 14 days. most frequently, children were under hospitalization for two days (32 / 26.9 %). 24 children (20.2 %) were inpatients for three days followed by 16 children (13.4) for four days and 14 children (11.8 %) for one day. A small number of eight children (6.7 %) had to stay in the hospital for five and seven days. Hospitalization for six and eight days was documented in four children (3.4 %). An inpatient treatment of nine and eleven days was recorded for two children (1.7 %). One child (0.8 %) was institutionalized for twelve as well as for 15 days.

When distinguishing the length of stay before and after the lockdown, no statistically significant difference could be detected ($P = 0.910$).

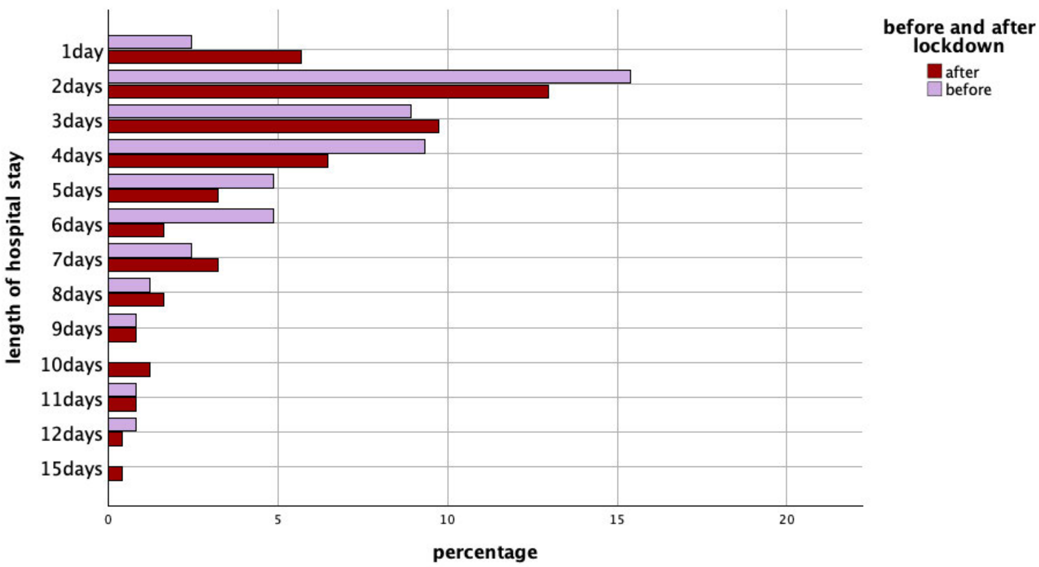

Figure 9. Length of hospital stay in patients with bronchiolitis before and after the lockdown
Data are presented as percentage

Note: 13 and 14 days of length of hospital stay are not mentioned in the figure because no patients were presented for both numbers of days

As showed in Table 3, the minimum of length of hospital stay for the period before and after the lockdown was one day. The maximum of length before the lockdown was twelve days and after lockdown 15 days. The mean length of hospital stay before the lockdown was reported as 3.92 ± 2.29 days and after the lockdown 3.89 ± 2.73 days. By analyzing and comparing the median value of the length of stay before and after the lockdown, a result of three days was obtained in both periods.

$P = 0.910$ indicated no statistical significance.

Table 3. Minimum, maximum, mean, and standard deviation of length of hospital stay of patients with bronchiolitis before and after the lockdown

length of hospital stay	minimum	maximum	median	mean	standard deviation	P^c
before lockdown	1 day	12 days	3.00 days	3.92 days	2.29 days	0.910
after lockdown	1 day	15 days	3.00 days	3.89 days	2.73 days	

[c] wilcoxon-mann-whitney test: $P < 0.05$ would be statistically significant

4.2 Sociodemographic facts

4.2.1 Sex

The sex distribution of patients hospitalized due to bronchiolitis before and after the lockdown is demonstrated in Figure 10. Before the lockdown, 81 children (63.3 %) were male and 47 (36.7 %) were female. After the lockdown, 66 young patients (55.5 %) were male and 53 (44.5 %) were female.

No statistically significant difference was found in the sex of children presenting with bronchiolitis ($P = 0.211$).

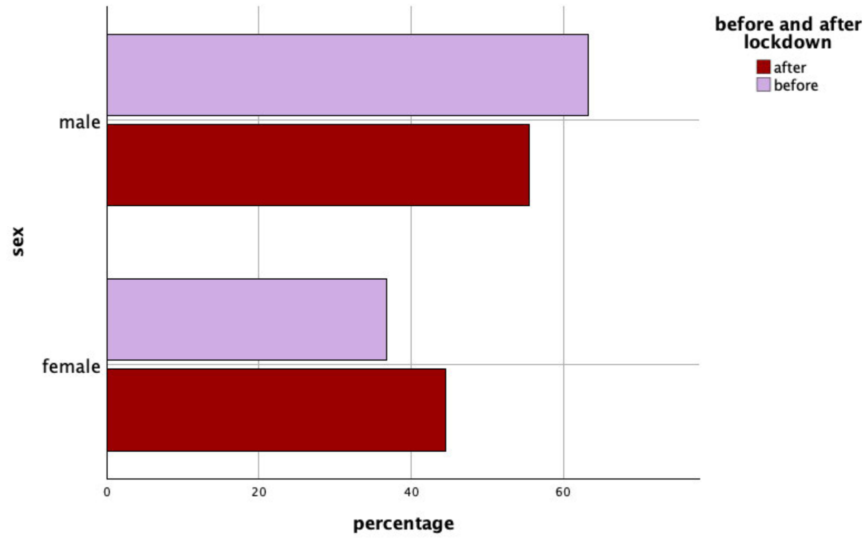

Figure 10. Sex of patients with bronchiolitis before and after the lockdown
Data are presented as percentage

4.2.2 Age

The age groups of the studied children are shown in Figure 11. Before the lockdown, the majority of children (51 / 39.8 %) were aged 29 days to less than three months who presented to the hospital for bronchiolitis. The second most common group was from six months to less than nine months with a total of 31 children (24.2 %). 13 newborns (10.2 %) were younger than 29 days. 27 pediatric patients (21.1 %) belonged to the group of three months to less than six months. Only six children (4.7 %) were aged nine months to less than twelve months. After the lockdown, most children (44 / 37.0 %) could be assigned to the group of 29 days to less than three months. The second most common group was from three to less than six months with a number of 36 young children (30.3 %). 19 pediatric patients (16.0 %) were younger than 29 days. The six to less than nine months group included 14 children (11.8 %). Only six children (5.0 %) were nine to less than twelve months of age.

No statistically significant difference could be observed in various groups of age before and after the lockdown ($P = 0.060$).

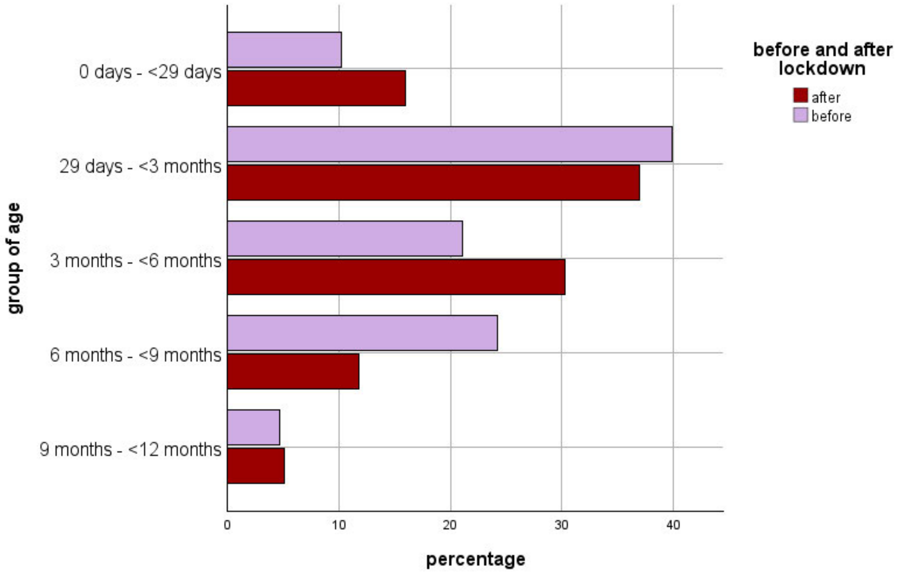

Figure 11. Group of age of patients with bronchiolitis before and after the lockdown
Data are presented as percentage

More details about the age of the studied population are presented in Table 4. Before the lockdown, the youngest child was 18 and the oldest child 342 days of age. On average, the children were 120.17 ± 86.90 days old. The median value was 91 days of age in patients studied before the lockdown. After the lockdown, the mean age was 105.21 ± 80.79 days and the youngest child enrolled was nine and the oldest child 360 days old. On examination of the median value, an age of 86 days resulted.

When comparing data before and after the lockdown, the outcome was not statistically significant (*P* = 0.249).

Table 4. Minimum, maximum, mean, and standard deviation of age of patients with bronchiolitis before and after the lockdown

age	minimum	maximum	median	mean	standard deviation	P^c
before lockdown	18 days	342 days	91.00 days	120.17 days	86.90 days	0.249
after lockdown	9 days	360 days	86.00 days	105.21days	80.79 days	

[c] wilcoxon-mann-whitney test: *P* < 0.05 would be statistically significant

4.3 Severity of bronchiolitis

4.3.1 Bacterial superinfection

The frequency of bacterial superinfection before and after the lockdown can be seen in Figure 12. Bacterial superinfection was detected in only 14 out of 247 pediatric patients in the studied population. Nine (7.0 %) of these 14 bacterial superinfections were documented in the period before the lockdown. The remaining five (4.2 %) were diagnosed in the time after the lockdown. 233 patients had no bacterial superinfections. 119 of these (93.0 %) were recorded before and 114 (95.8 %) after the lockdown.

A *P*-value of 0.337 indicated that there was no statistically significant discrepancy

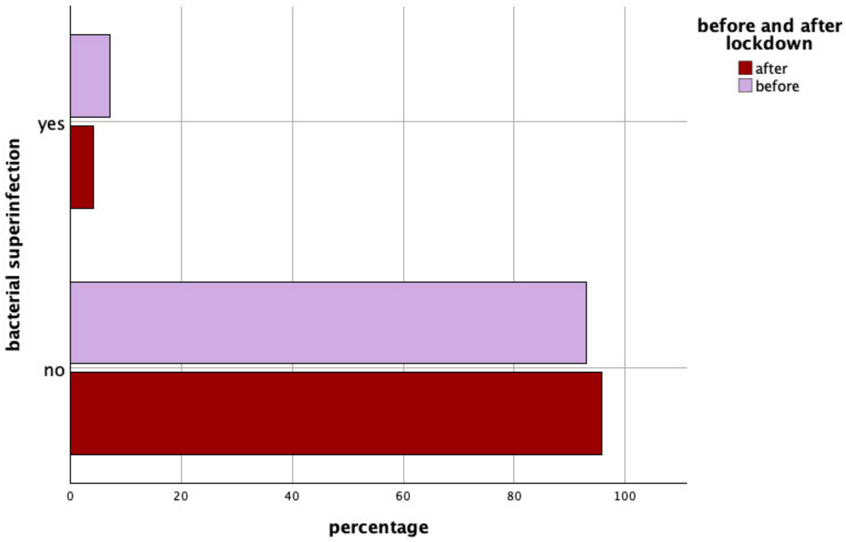

Figure 12. Bacterial superinfection in patients with bronchiolitis before and after the lockdown
Data are presented in percentage

The likelihood of bacterial infection occurring in a young patient with bronchiolitis is not associated with the lockdown (odds ratio (OR) 0.554, 95 % confidence interval (CI) 0.178-1.721), sex (OR 0.832, 95 % CI 0.268-2.586), or age (OR 0.217, 95 % CI 0.988-1.003), as it is represented in Table 5. The risk of suffering from a bacterial superinfection before the lockdown is 44.6 % lower than after the lockdown. Girls are 16.8 % less likely to acquire a bacterial superinfection than boys.

When investigating whether lockdown, sex and age are associated with the occurrence of bacterial superinfection, no statistically significant difference was obtained ($P = 0.307$, $P = 0.751$, $P = 0.217$).

Table 5. Logistic regression of bacterial superinfection

bacterial superinfection	P^d	OR	95 % CI
before vs. after lockdown	0.307	0.554	0.178–1.721
female vs. male	0.751	0.832	0.268–2.586
age (in days)	0.217	0.995	0.988–1.003

This table shows the results of the logistic regression with the dependent variable bacterial superinfection (yes/no) and the independent variables before/after the lockdown, sex and age.
[d] $P < 0.05$ would be statistically significant

4.3.2 Oxygen therapy

The need for oxygen therapy is visualized in Figure 13. In the studied population, a total of 107 (43.3 %) of 247 patients required oxygen therapy during their hospitalization for bronchiolitis. Before the lockdown, 49 children (38.3 %) received oxygen, and after the lockdown, 58 children (48.7 %) were in need of oxygen. 140 children (56.7 %) did not require any oxygen. Of these, 79 (61.7 %) children were documented before and 61 children (51.3 %) after the lockdown.

A *P*-value of 0.097 demonstrated no statistically significant discrepancy.

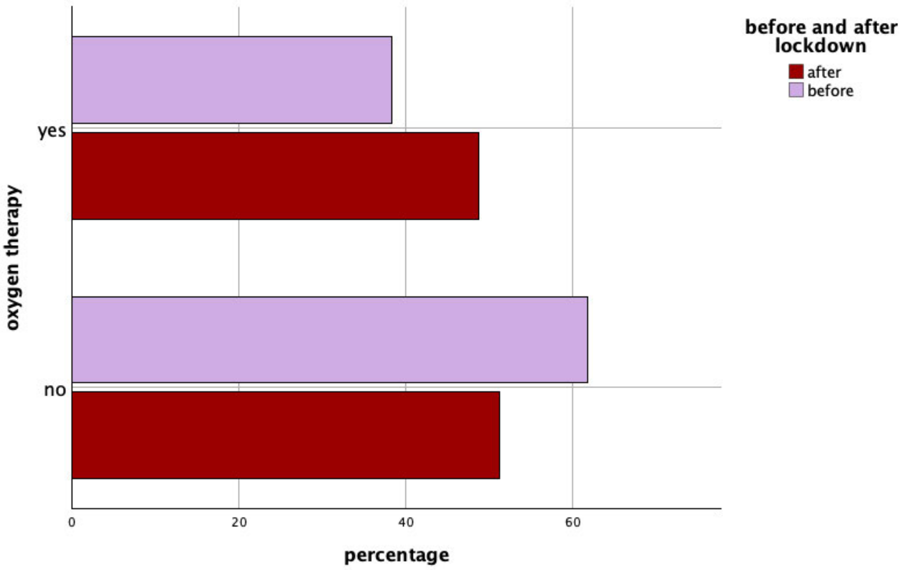

Figure 13. Need for oxygen therapy in patients with bronchiolitis before and after the lockdown
Data are presented in percentage

As shown in Table 6, no association exists between the need for oxygen therapy and lockdown (OR 0.678. CI 95 % 0.407-1.130), sex (OR 0.755, CI 95 % 0.450-1.267), and age (OR 0.999, CI 95 % 0.996-1.002). When investigating the influence of the lockdown on oxygen demand in infants, it was found that the likelihood of needing oxygen was 32.2 % lower before than after the lockdown. Girls were about 24.5 % less likely to need oxygen.

Likewise, no statistically significant discrepancy is seen with regard to these variables ($P = 0.136$, $P = 0.228$, $P = 0.389$).

Table 6. Logistic regression of oxygen therapy

oxygen therapy	P^d	OR	95 % CI
before vs. after lockdown	0.136	0.678	0.407–1.130
female vs. male	0.228	0.755	0.450–1.267
age (in days)	0.389	0.999	0.996–1.002

This table shows the results of logistic regression with the dependent variable oxygen therapy (yes/no) and the independent variables before/after the lockdown, sex and age.

[d] $P < 0.05$ would be statistically significant

4.3.3 Mechanical ventilation/respiratory support

Figure 14 describes the need for mechanical ventilation/respiratory support. Of 247 children, ten children (4 %) in total required mechanical/respiratory support, and 237 children (96 %) were managed without any assistance. Before the lockdown, two children (1.6 %) and after the lockdown, eight children (6.7 %) needed assistance. 126 pediatric patients (98.4 %) before and 111 pediatric patients (93.3 %) after the lockdown did not require any assistance.

However, no statistically significant mismatch could be shown ($P = 0.053$).

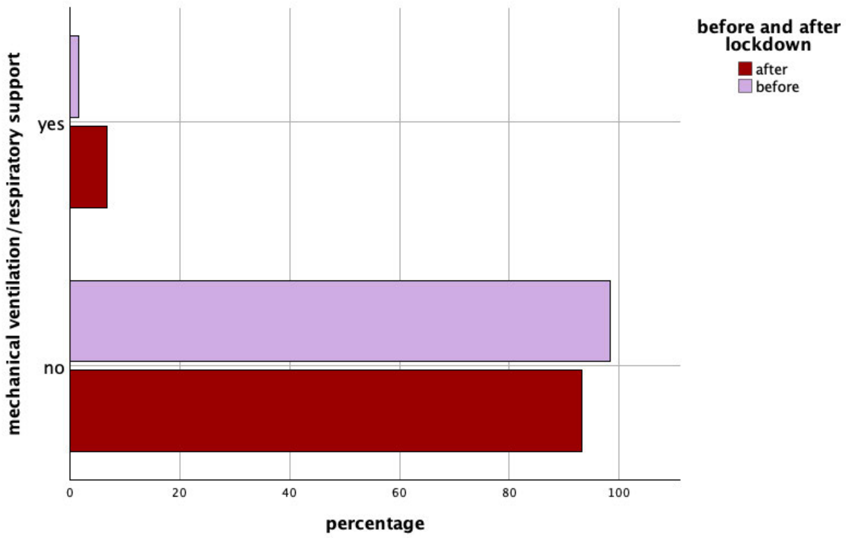

Figure 14. Need for mechanical ventilation/respiratory support in patients with bronchiolitis before and after the lockdown
Data are presented in percentage

Regarding the dependency on mechanical ventilation/respiratory support, no association of lockdown (OR 0.258, CI 95 % 0.051-1.307) and sex (OR 0.717, CI 95 % 0.183-2.804) was found, as demonstrated in Table 7. However, age presents a significant association with the need for mechanical ventilation/respiratory support (OR 0.965, CI 95 % 0.940-0.991). A more precise inspection of the OR reveals that the need for mechanical ventilation/respiratory support was 74.2 % less likely before than after the lockdown. Female patients were 28.3 % less likely to demand for mechanical ventilation/respiratory support than males. The odds of necessitating mechanical ventilation/respiratory support in older patients were 3.5 % less likely than in younger children.

No statistically significant difference was reported between the need of mechanical ventilation/respiratory support and lockdown and sex ($P = 0.102$, $P = 0.633$) except the age with $P = 0.010$.

Table 7. Logistic regression of mechanical ventilation / respiratory support

mechanical ventilation/respiratory support	P^d	**OR**	**95 % CI**
before vs. after lockdown	0.102	0.258	0.051–1.307
female vs. male	0.633	0.717	0.183–2.804
age (in days)	**0.010**	0.965	0.940–0.991

This table shows the results of the logistic regression with the dependent variable mechanical ventilation/respiratory support (yes/no) and the independent variables before/after the lockdown, sex and age.

[d] $P < 0.05$ would be statistically significant

4.3.4 Intensive care unit

The final factor assessed for the severity of childhood bronchiolitis was the need for ICU. These details can be reviewed again in Figure 15. Among 247 children, 27 (10.9 %) patients required intensive care, eight (6.2 %) before and 19 (16.0 %) after the lockdown.

With a *P*-value of 0.014, a statistically significant difference was demonstrated between before and after lockdown with regard to intensive care.

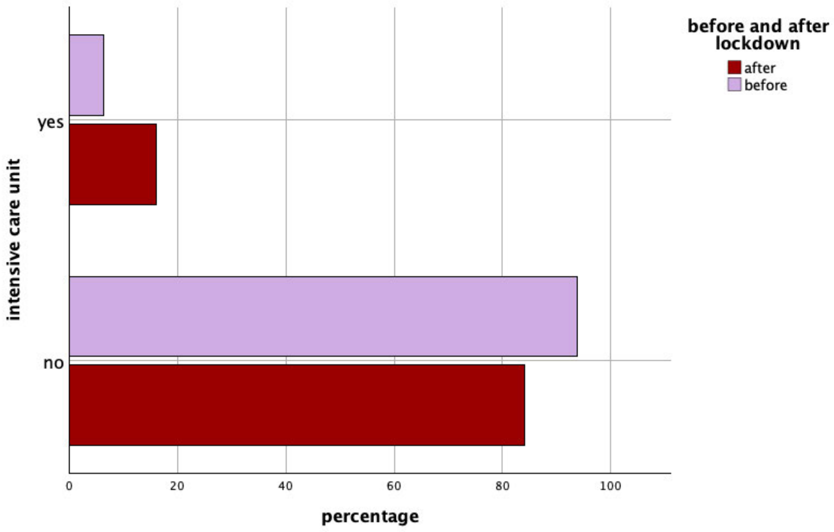

Figure 15. Need for intensive care unit in patients with bronchiolitis before and after the lockdown
Data are presented in percentage

The need for intensive care treatment was analyzed again specifically for the association with lockdown, sex and age. In this evaluation, both lockdown and age (in days) were found to have a direct and significant effect on the occurrence of ICU care (lockdown: OR 0.393, CI 95 % 0.161-0.960; age: OR 0.988, CI 95 % 0.979-0.996). The association is statistically significant which was confirmed by the p-values for lockdown and ICU (P = 0.040) as well as age and ICU (P = 0.003). Based on the analyses and OR = 0.39, it can be shown that the probability of receiving intensive care before the lockdown was 60.7 % lower than after the lockdown. Children at older age were 1.2 % less likely to receive intensive care than younger children. However, the small number of samples (N) should be considered and taken into account in the analysis.

On the contrary, by studying the influence of sex on the need for treatment in the intensive care unit, no significant relationship was observed. Also, no statistically significant difference was established between sex and intensive care unit (P = 0.331). Girls were 34.0 % less likely than boys to access more intensive care than before the lockdown. Table 8 summarizes these results briefly again.

Table 8. Logistic regression of intensive care unit

intensive care unit	P^{d}	OR	95 % CI
before vs. after lockdown	**0.040**	0.393	0.161–0.960
female vs. male	0.331	0.660	0.285–1.526
age (in days)	**0.003**	0.988	0.979–0.996

This table shows the results of the logistic regression with the dependent treatment in intensive care unit (yes/no) and the independent variables before/after the lockdown, sex and age.

[d] $P < 0.05$ would be statistically significant

5. DISCUSSION

During the corona pandemic, measures such as hand hygiene, face masks, spacing were introduced to reduce the spread of this disease. After the dissolution of these non-pharmaceutical interventions, a sharp increase in infections has been expected. This assumption was mainly due to the lack of immune stimulation caused by the absent circulation of viruses and the lack of memory of the immune system to these viral pathogens. Consequently, the immune system is fragile and susceptible to infections (48). Our hypothesis that the lockdown negatively affects the severity of bronchiolitis in children younger than one year of age was partially confirmed with this study.

Hospitalization rate

Bronchitis, bronchiolitis, and pneumonia represent the lower respiratory tract infections in children (49-51). Among these three, bronchiolitis is the most common disease leading to emergency department presentations and hospitalization (52). This statement is consistent with our findings. In both periods including before and after the lockdown, the majority of children presenting to the emergency department were admitted and treated in the hospital due to bronchiolitis as diagnosis of discharge. Prior to the covid-19 pandemic or lockdown, the total number of hospitalizations due to suspicion of bronchiolitis in children was slightly higher in our studied population than after the lockdown. Hospitalization rates were also slightly greater before the lockdown, in contrast to the literature. One study was able to show an increased hospitalization rate of children with bronchiolitis after relative to before the lockdown (53). However, we were not able to support this finding with our study results, although we actually expected an increased rate. This statement is based on the assumption that due to the lockdown and lower circulation of pathogens, the immunity of children after the covid-19 pandemic is weak and leads to more infections (54).

Virus

Bronchiolitis in childhood is a condition most typically caused by a respiratory infection that is viral in nature (55). RSV is the leading viral pathogen, accounting for around 80 % of all cases in children younger than one year of age followed by hMPV (3-19 %) and hRV (20 %) (24,56). Our study yielded similar results in the studied population before the lockdown. Higher proportions of RSV was detected in the period after the lockdown confirmed by another scientific work (57). Further study also found RSV to be the most common viral pathogen (75 %) followed by hRV (48). The latter mentioned etiological agent was the second most frequent pathogen in our patients. This finding can possibly be explained by the fact that the children have been tested more frequently for RSV and other pathogens after the lockdown (58). However, it must be recalled that the numbers of each pathogen are very small and the amount of RSV infections detected is not drastically divergent.

SARS-CoV-2 and Coronavirus OC43 accounted for only a minority in our study in the after-lockdown period. Other studies support our result with 1.6 % for SARS-CoV-2 emphasizing its rarity (48,53). One justification for this is the lower risk of children being infected with SARS-CoV-2. This statement is based on the hypothesis of other studies that children are protected from this kind of over-inflammatory condition. The underlying factor is the age difference in the extent of variation in the expression of angiotensin converting enzyme 2 (ACE2) in several tissues compared to adults (59). PIV 3 had been detected once after the lockdown. In contrast, hMPV was more likely identified before than after the lockdown. Similar results were obtained in another study (57). In some children, no pathogen could be detected at all. The test was more often negative before than after the lockdown. This tendency can be confirmed by other published studies (23 % vs. 19.2 %) (48,60). Our hypothesis for addressing this issue is that multiplex PCR was probably performed more frequently in our hospital after the lockdown, rather than RSV testing alone. However, we did not focus on this point in our study and thus cannot prove this hypothesis.

Coinfection

In patients with bronchiolitis, the causative infection may involve not just one, but several viruses. In 10-30 % of pediatric children, coinfections can be detected. RSV together with hMPV or hRV are the most frequent types of coinfections (61,62). In our analysis, we found only a small number of coinfections both before and after the lockdown (rarity). These were spotted using a multiplex PCR. Almost 97 % of pediatric patients were tested negative before and 98 % after the lockdown. Before the lockdown, RSV and Influenza A/H1-2009 was the most common isolated coinfection. After the lockdown, RSV and hRV/EV was the variant most often documented. In other scientific researches, different results emerged, compared to our results. These studies have documented a higher level of coinfection caused by more than one virus after the lockdown (57). Two studies, as examples, revealed the rate of coinfections above 10 % (13.5 %, 19.9 %) (48,63). Most coinfections were reported between RSV and RV (64). Our low percentage may be due to the fact that multiplex PCR was not performed on every child and thus not tested for all viruses. The low rate of multiplex PCR might be responsible for the poor level of coinfections.

Month of admission

RSV-bronchiolitis is a viral disease that presents seasonally. The first children with bronchiolitis are seen in October. The highest level of cases shows up in January and February. The season terminates in April (9). Indeed, this epidemiologic occurrence of RSV-bronchiolitis could be reproduced in our children hospitalized and studied before the lockdown. The first few cases were dated in September and increased steadily through the winter months. The highest levels were recorded in January and February. In the following months, until May, the rate slowly dropped. Covid-19 pandemic and its ensuing lockdown have defeated a change in the seasonal incidence of RSV-bronchiolitis as can be seen in our results of the time after the lockdown. After the lockdown, the first infected children presented to the pediatric emergency department already in the summer months concerning respiratory complaints. The number increased continuously. The peak was reached in November (38.7 %). From December on, the trend was downwards again with isolated cases in January to March. A study from Italy presented analogous alterations in the occurrence of the bronchiolitis season. Here, too, the first cases were diagnosed during the summer months (July and August). Incidence of the disease increased significantly in October. In November and early December, the peak was also attained here, followed by an abrupt decline at the end of December. In January and February, only a few sick children were documented in Italy as well. In Italy, the duration of the season was also shorter compared to the period before covid-19 (48). This statement cannot be confirmed with our results. Another study, conducted at two pediatric university hospitals in Regensburg from 2016 until 2022, also showed an alternating rhythm of the RSV season, which is in agreement with our findings (65). In conclusion, the covid-19 pandemic and lockdown affected the season to start and stop earlier as well as to peak in November, not January as usual and mentioned before. Our assumption is that the underlying cause of this seasonal shift lies in the unwinding of the corona restrictions including facial masks, hand hygiene and social distancing as examples, which took place in May 2021 (47,66). From there, the virus had been able to spread again and attack children whose immune system was weak and not well-developed due to the lockdown and missing infections (54,67).

Length of hospital stay

A single-center retrospective study conducted from 2001 to 2019 examined the length of stay in hospital of children younger than two years with bronchiolitis and what factors may influence this parameter. In this analysis, they concluded that the length of stay on hospital was mostly in the region of 2.5 to 3 days. This result is consistent with our data (68). By comparing before and after the lockdown, we were not able to find any difference in the length of stay of children with bronchiolitis, supported by data from a separate survey (57). In both cases, the average was three days and majority of the children remained hospitalized for two days. In our opinion, the length of stay should have been prolonged comparing before and after the lockdown. To establish a discordance, it may be necessary to evaluate other variables that may influence the length of stay, such as oxygen saturation, fever, gestational age, and birth weight (68). However, this could not be validated and explained with our outcomes.

Sex

Studies have verified that boys have a higher risk of contracting a respiratory infection (pneumonia, asthma, bronchitis, bronchiolitis and upper respiratory tract infections) compared with girls, regardless of birth-related features such as gestational age and birth weight. The likelihood of developing a severe bronchiolitis is higher in boys mainly due to variations in pulmonary and respiratory tract development as well as genetic determinants (9,69). In the study we conducted, boys were the most affected in both periods. This statement is in agreement with the previously mentioned researches. However, in the post-lockdown period, the difference between boys and girls decreased. Consequently, proportionally more girls and fewer boys were affected. We cannot properly interpret this result, as there are possible explanations that would support the opposite outcome. The findings of another study are able to show that more boys than girls are targeted after the lockdown, with a statistical significance (53). Overall, it may be noted that some inconsistencies exist between studies, as according to one research there is no difference at all in terms of gender (57).

Group of age

At the beginning of their lives, newborns and infants still receive immunological assistance via antibodies from their mothers through placenta and/or breast milk transfer. Gradually, the maternal antibodies break down and the child's immune system has to cope on its own (70-72). This is one possible factor why at the age of two to three months (some studies say up to five months), the rate of infections is the highest (24,73). In our study, the children with bronchiolitis from 29 days to three months of age constituted the largest proportion of all age groups independently of the lockdown which is consistent with the previous statements. The distribution of the fraction of each age group was shifted slightly after the lockdown. As mentioned at the beginning, most were in the age range of 29 days to less than three months

(39.8 %), followed by six to less than nine months and three to less than six months. After the lockdown, the overall distribution remained the same, but more younger children were affected in total. 16.0 % of children were younger than 29 days. This shift toward younger age, reported by our results, is plausible as younger age plays a risk factor for infection, especially for a severe course (61,73). The underlying issue is the immaturity and vulnerability of the immune system of newborns and young children (70,71). Therefore, we expected these kinds of outcomes.

Severity of bronchiolitis

We investigated the severity of bronchiolitis in children aged under one year using four different parameters: bacterial superinfection, oxygen therapy, mechanical ventilation / respiratory support, and intensive care. We compared the variables before and after the lockdown to detect any potential deviations. The resulting differences in these parameters are based on the impaired immunity of pediatric patients as a consequence of the covid-19 pandemic (54).

Bacterial superinfection

In the period before the lockdown, only 7% of the patients had a proven bacterial superinfection. This result is very descriptive of what is also widely reported in the literature: bacterial superinfection in children with bronchiolitis is a scarcity (3). After the lockdown, the incidence of bacterial superinfection was even lower. According to our study, the appearance of bacterial superinfection is independent of lockdown, sex, or age. However, based on the literature, this statement is not completely justifiable. First, the lower age that prevailed in the post-lockdown period, should increase the likelihood of superinfection. Based on our results, we can only say that younger children were 0.05 % more likely to be affected by bacterial superinfection than older children, so virtually no difference. Second, given the developmental differences of the pulmonary system, boys should be more frequently affected. This issue can be supported by our study presenting that girls have a 16.8 % lower risk of acquiring bacterial superinfection than boys. Further studies need to be performed to obtain more precise information and correlations.

Oxygen therapy

Oxygenation and hydration are two points that are very crucial in the therapy of bronchiolitis in children. Consistent with our expectation, the proportion of children who needed oxygen increased to 48.7 % after the lockdown. The children in this study were younger and thus more susceptible to a heavier course of bronchiolitis in the post-lockdown period. Accordingly, this circumstance increased the likelihood of oxygen therapy. However, no statistical significance could be demonstrated for the difference. The deviation is likely, but not meaningful due to the small number of patients. Our results also must be taken with a magnitude of concern, as we included any need for oxygen in our analysis. We did not take care about the duration of oxygen therapy. In order to interpret the data more accurately, it would be better in the future to divide the oxygen requirement precisely and evaluate it then.

Mechanical ventilation/respiratory support

As another factor of severity, we explored the need for mechanical ventilation/respiratory support in children with bronchiolitis before and after the lockdown. We included all children in the study who received high-flow oxygen therapy, CPAP, or were on invasive ventilation. We found no major differences between these two periods, as did another study (57). The number of affected children increased from 1.6 % to 6.7 %. Accordingly, the trend is upward with rising demand for mechanical ventilation/respiratory support. This tendency is arguable with the scientific background and the characteristics of the studied patients after the lockdown. The increased demand was mainly affected by age but was independent of lockdown and gender. Younger patients had the request more frequently than older ones. This statement is consistent with the literature. Other studies have divided this parameter into need for oxygen low flow, oxygen high flow, CPAP, and mechanical ventilation (48). One study reported the need for invasive mechanical ventilation in 2-3 % of children. Due to our classification, we cannot correctly compare this percentage with ours (74). This division makes sense to achieve more precise, detailed and comprehensible results. Accordingly, it is not easy to compare our results with others and it should be kept in mind when interpreting.

Intensive care unit

2-6 % of all children hospitalized for bronchiolitis require treatment in the ICU. Some studies report 10 % or 13 % of ICU admissions (23,74). Our outcomes in the period before the lockdown are consistent with these percentages. Higher rate of ICU admissions was observed in the studied population after the lockdown as confirmed by another study presenting similar tendency (57). Almost twice as many children as before the lockdown had to be treated in the ICU. Our tests showed that the necessity of intensive care treatment was dependent on lockdown and age, whereas sex did not play any role. As with the parameters discussed previously, the characteristics of the pediatric patients studied after the lockdown had a fundamental effect on the need for intensive care.

Limitations

Our performed study has a couple of limitations. We focused only on children under one year of age. However, depending on the country, the definition of bronchiolitis includes children up to two years of age. Accordingly, many studies have investigated children under the age of two years. As a result, we were not able to show decisive outcomes for every parameter, especially with significant difference that can be compared with the findings of other studies. Our groups being compared (before and after the lockdown) were not of the same size (128 vs. 119). Consequently, it is important to take this aspect into account when interpreting and applying the results as some data may give an incorrect impression due to mismatch in quantity. Furthermore, we focused only on bronchiolitis. Nevertheless, lower respiratory tract infections consist of pneumonia, bronchitis, and bronchiolitis. If all three conditions were considered, more significant and accurate results could emerge. In addition, it is often difficult to distinguish bronchitis from bronchiolitis in young children because many symptoms overlap. Hence, we may not have caught all children with bronchiolitis leading to missing or incorrect data. Another big limitation is that our subgroups are also often very small. This leads to results giving a false impression. It should be included in the interpretation of some findings in order to evaluate the results correctly. It would have been advantageous if the total population had been larger and thus also the subgroups in order to obtain better and more meaningful information.

6. CONCLUSION

- The hospitalization rate of children aged younger than one year with bronchiolitis was minimally lower after than before the lockdown. The number of children hospitalized due to suspicion of bronchiolitis was independent of the lockdown.
- RSV was the most common viral pathogen detected both before and after the lockdown followed at a wide margin by hRV/EV. After the lockdown, it was documented more often as a viral cause. This result was statistically significant. SARS-CoV-2 was detected as a minority only in the post-lockdown period. Prior to the lockdown, more children were admitted without traceable virus.
- Coinfection was of no relevance both before and after the lockdown.
- The epidemiological season of bronchiolitis, mainly due to RSV, changed drastically by the lockdown, confirmed by a statistically significant difference. It started already in summer months, dramatically increased from October to November with its highest point in November. Few cases were documented in January and February. Before the lockdown, the season went from November to April with peak point in January and February.
- The lockdown had no effect on the length of stay in the hospital. In both periods, the average length of stay was four days. The majority of children were hospitalized for two days in both phases.
- Boys were more frequently affected in both terms with decrease after the lockdown, no statistical significance detectable. However, the proportion of girls increased in the period after the lockdown.
- The majority of children were aged 29 days to less than three months in both periods assessed. On average, children with bronchiolitis were younger during the post-lockdown period than before the lockdown. More children younger than 29 days were identified. This difference narrowly missed statistical significance.
- The occurrence of bacterial superinfection was independent of lockdown, sex and age. It could be diagnosed more frequently in the period before the lockdown than afterwards, which contradicts our hypothesis.
- The urgency for oxygen therapy in children with bronchiolitis was larger after than before the lockdown. However, according to our studies, the requirement for oxygen was not dependent on lockdown, sex, and age.
- The children with bronchiolitis needed more mechanical ventilation/respiratory support after the lockdown. This result was just barely not statistically significant. The need for

respiratory support was not influenced by lockdown and gender, but age clearly mattered.

- After the lockdown, more children with bronchiolitis required ICU treatment, emphasized by evidenced statistical significance. The necessity of intensive care treatment was significantly dependent on lockdown and age of the child. Sex did not contribute to the results.

In brief, our studies have shown a tendency toward increased severity of bronchiolitis in children younger than one year of age after the lockdown, in contrast to other studies (39,49).

Unfortunately, we cannot present many results with significant differences, but a discrepancy between these two periods depending on the lockdown can be highlighted for several parameters.

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8. SUMMARY

Objectives: The purpose of this study was to evaluate differences in the severity of bronchiolitis in children younger than one year of age before and after the lockdown caused by the covid-19 pandemic.

Materials and methods: This retrospective study examined children up to 365 days of age hospitalized for bronchiolitis in two periods, classified by before and after the lockdown: from 1st of April, 2018 until 31st of March, 2020 and from 1st of May, 2021 until 30th of April, 2023. Focus was placed on the influence of the lockdown on the severity of bronchiolitis in children younger than one year of age. We analyzed the following parameters: general information of the studied children (hospitalization rate of bronchiolitis, virus, coinfection, monthly admission, length of stay in hospital), socio-demographic data (sex, age) and the severity of bronchiolitis (bacterial infection, oxygen therapy, mechanical ventilation/respiratory support, intensive care unit).

Results: Our survey consisted of 323 children comprising 163 before and 160 children after the lockdown. After screening for the diagnosis of bronchiolitis, our study included only 247 children who were used for the further major examinations. 128 children of them belonged to the period before the lockdown, the remaining 119 children participated in the period after the lockdown. RSV was the most common detectable viral agent in both phases with an increase in the post-lockdown period (72.7 % vs. 84.0 %; $P = 0.021$). Seasonal occurrence of bronchiolitis, specifically RSV-bronchiolitis, shifted due to the lockdown ($P < 0.001$). First cases were documented in the summer and early fall months with peak in November (0.0 % vs. 38.7 %). Few cases were recorded in January and February (21.1 % vs. 4.2 %, 39.8 % vs. 1.7 %). More boys were affected in both periods, but with a decreasing trend in the post-lockdown phase (63.3 % vs. 55.5 %, $P = 0.211$). On average, studied children were younger after the lockdown (120 ± 87 days vs. 105 days ± 81 days, $P = 0.249$), with an increase in children younger than 29 days (10.2 % vs. 16.0 %). During both eras, the majority of patients studied were 29 days to less than three months of age (39.8 % vs. 37.0 %, $P = 0.060$). Bacterial superinfections were detected more frequently before the lockdown (7.0 % vs. 4.2 %, $P = 0.337$).The necessity of oxygen therapy was more apparent in the children after the lockdown (38.3 % vs. 48.7 %), even though without statistical significance ($P = 0.097$). The latter two parameters were independent of lockdown, sex and age of the patient. The occurrence of mechanical ventilation/respiratory support was more often after the lockdown (1.6 % vs. 6.7 %) and significantly associated with age ($P = 0.010$), but again without statistical significance (*P* = 0.053). Following the lockdown, more children required intensive care and treatment (6.2 % vs. 16.0 %, *P* = 0.014), significantly influenced by lockdown and age (*P* = 0.040, *P* = 0.003). Our study achieved no difference in the case of coinfection (1.6 % vs. 1.7 %) and length of hospital stay (two days most frequently, 4 days ± 2 days and 4 days ± 3 days on average).

Conclusion: The introduction and subsequent enactment of the lockdown with its associated NPIs have an impact on the severity of bronchiolitis in pediatric patients. Upward trends concerning oxygen therapy, mechanical ventilation/respiratory support, and intensive care could be demonstrated. However, further studies are needed to investigate the severity of bronchiolitis in children under the influence of the lockdown in more detail, with greater precision and in a larger population.

9. CROATION SUMMARY

Naslov: Razlike u težini bronhiolitisa među novorođenčadi i dojenčadi mlađom od jedne godine prije i nakon zaključavanja zbog pandemije COVID-19.

Ciljevi: Svrha ovog istraživanja bila je procijeniti razlike u težini bronhiolitisa u djece mlađe od godinu dana prije i nakon zaključavanja uzrokovanog pandemijom covid-19.

Materijali i metode: Ova retrospektivna studija ispitivala je djecu do 365 dana starosti hospitaliziranu zbog bronhiolitisa u dva razdoblja, klasificirana prije i nakon zaključavanja: od 1. travnja 2018. do 31. ožujka 2020. i od 1. svibnja 2021. do 30. travnja 2023. Fokus je stavljen na utjecaj zaključavanja na ozbiljnost bronhiolitisa u djece mlađe od godinu dana. Analizirali smo sljedeće parametre: opće podatke ispitivane djece (stopa hospitalizacije bronhiolitisa, virusa, koinfekcije, mjesečni prijem, duljina boravka u bolnici), sociodemografske podatke (spol, dob) i težinu bronhiolitisa (bakterijska infekcija, terapija kisikom, mehanička ventilacija/respiratorna podrška, jedinica intenzivne njege).

Rezultati: Istraživanje se sastojalo od 323 djece koja su se sastojala od 163 djece prije i 160 djece nakon zaključavanja. Nakon probira za dijagnozu bronhiolitisa, naša studija je uključila samo 247 djece koja su korištena za daljnje velike preglede. Njih 128 djece pripadalo je razdoblju prije zaključavanja, preostalih 119 djece sudjelovalo je u razdoblju nakon zaključavanja. RSV je bio najčešći virusni agens koji se može otkriti u obje faze s povećanjem razdoblja nakon zaključavanja (72,7 % naspram 84,0 %; P = 0,021). Sezonska pojava bronhiolitisa, posebno RSV-bronhiolitisa, pomaknuta je zbog zaključavanja (p < 0,001). Prvi slučajevi zabilježeni su u ljetnim i ranim jesenskim mjesecima, a vrhunac je zabilježen u studenome (0,0 % naspram 38,7 %). U siječnju i veljači zabilježeno je nekoliko slučajeva (21,1 % naspram 4,2 %, 39,8 % naspram 1,7 %). U oba su razdoblja oboljeli više dječaka, ali s trendom smanjenja u fazi nakon zatvaranja (63,3 % u odnosu na 55,5 %, P = 0,211). U prosjeku, ispitivana djeca bila su mlađa nakon zaključavanja (120 ± 87 dana u odnosu na 105 dana ± 81 dan, P = 0,249), s povećanjem broja djece mlađe od 29 dana (10,2 % naspram 16,0 %). Tijekom oba razdoblja, većina ispitanih pacijenata bila je u dobi od 29 dana do manje od tri mjeseca (39,8 % naspram 37,0 %, P = 0,060). Bakterijske superinfekcije otkrivene su češće prije zaključavanja (7,0 % naspram 4,2 %, P = 0,337). Potreba za terapijom kisikom bila je očitija u djece nakon zatvaranja (38,3 % naspram 48,7 %), iako bez statističke značajnosti (P = 0,097). Potonja dva parametra bila su neovisna o zaključavanju, spolu i dobi pacijenta. Pojava mehaničke ventilacije/respiratorne potpore bila je češća nakon zaključavanja (1,6 % naspram

6,7 %) i značajno povezana s dobi (p = 0,010), ali opet bez statističke značajnosti (*P* = 0,053). Nakon zatvaranja više djece zahtijevalo je intenzivnu njegu i liječenje (6,2 % u odnosu na 16,0 %, *P* = 0,014), pod znatnim utjecajem ograničenja kretanja i dobi (*P* = 0,040, *P* = 0,003). U ovom istraživanju nije postignuta razlika u slučaju koinfekcije (1,6 % naspram 1,7 %) i duljini boravka u bolnici (dva dana najčešće, 4 dana ± 2 dana i 4 dana ± 3 dana u prosjeku).

Zaključci: Uvođenje i naknadno donošenje zaključavanja s povezanim NPI-ima utječe na ozbiljnost bronhiolitisa u pedijatrijskih bolesnika. Mogli bi se pokazati uzlazni trendovi u vezi s terapijom kisikom, mehaničkom ventilacijom / respiratornom podrškom i intenzivnom njegom. Međutim, potrebna su daljnja istraživanja kako bi se detaljnije istražila ozbiljnost bronhiolitisa u djece pod utjecajem zaključavanja, s većom preciznošću i u većoj populaciji.

10. CURRICULUM VITAE

GENERAL INFORMATION

name: [redacted]

address: [redacted]

born: [redacted]

nationality: [redacted]

EDUCATION

2017-2023	University of Split, School of Medicine (Regiomed), study program of medicine
2016-2017	University of Bremen, Bachelor Public Health

INTERNSHIPS

August 2023	internship in general medicine, [redacted]
January/February 2023	clinical rotations in general medicine/thoracic surgery/gynecology/pediatrics, [redacted]
September 2022	internship in internal/surgical emergency department, [redacted]
August 2022	internship in orthopedic rehabilitation clinic, [redacted]
August 2021	internship in general medicine, [redacted]
September 2020	internship in pediatrician's office, [redacted]
August 2019	internship in gastroenterology, [redacted]
September 2018	internship in spinal and neurosurgery, [redacted]

WORK EXPERIENCES

March-July 2023	working student, [redacted]
July 2022-February 2023	working student in sleeping laboratory, [redacted]
October 2019-June 2022	working student on nurse station, [redacted]

SCIENTIFIC EXPERIENCES

April 2021-today	PhD student at institute of general medicine, [redacted]