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INTEGRATED STUDY MASTER'S THESIS

Respiratory Syncytial Virus Infection in Neonates and Infants

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TABLE OF CONTENTS

LIST OF ABBREVATIONS

ADH - Anti diuretic hormone
ALRI - Acute lower respiratory infection
BPD - Bronchopulmonary dysplasia
CHD - congenital heart disease
COPD - Chronic obstructive pulmonary disease
ED - Emergency department
FDA - U.S Food and Drug Administration
GA - Gestational Age
HM - Hematologic malignancy
HSCT - Hematopoietic stem cell transplantation
ICU - Intensive Care Unit
LMICs - Low-Middle income countries
LRT - Lower respiratory tract
LRTI - Lower respiratory tract infection
mAb - Monoclonal antibodies
nAbs - Neutralizing antibodies
NPI - non-pharmaceutical interventions
PCR - Polymerase-chain-reaction
PTI - Preterm infant
qRT-PCR – Real- Time quantitative reverse transcription
RADTs - rapid antigen detection tests
RT-PCR - Reverse transcription polymerase chain reaction
RT-qPCR - reverse-transcription quantitative PCR
RSV - Respiratory syncytial virus
RSV F vaccine - RSV fusion (F) protein nanoparticle vaccine
RSVpreF - RSV stabilized prefusion F subunit vaccine
STIKO - Ständige Impfkommission (German vaccination program)
TdaP - Tetanus-Diphtheria-Pertussis
URTI - Upper respiratory tract infection

VUH SK - Vilnius University Hospital Santaros Klinikos
WBE - wastewater-based epidemiology

SUMMARY

Respiratory syncytial virus (RSV) is globally a leading cause of acute lower respiratory infections (ALRI), most often seen as bronchiolitis, in neonates and infants. The morbidity and fatality rates connected to RSV during infancy, especially for children that count to be at high risk, including preterm newborns and those with underlying medical disorders, highlight the importance of developing better prevention and treatment techniques. This thesis addresses the changing epidemiology of RSV infections, demonstrates the impact of COVID-19 and how the RSV occurrence pattern has changed and examines current and emerging immunoprophylaxis techniques in Lithuania and other northern hemisphere countries.

The primary goal of the study is to review the literature on neonatal and infant RSV infections, assess changes in seasonal trends at Vilnius University Hospital Santaros Klinikos (VUH SK), and compare immunoprophylaxis practices in Lithuania to international models, for example Germany. The goals include researching epidemiological, clinical, and preventative aspects of RSV, analyzing local incidence data from 2020 to 2025, and assessing immunoprophylaxis options.

Research of different literature was performed using databases such as PubMed, ResearchGate, and UpToDate, with a focus on papers published between 2020 and 2025. The most prominent key search terms included RSV, infants, bronchiolitis, seasonality, prevention, and immunoprophylaxis. Moreover, data from VUH SK and data from Germany, the United States, Spain, Italy, and Northern Ireland were used to assess the development of seasonal changes and immunization policies, allowing to illustrate similarities and differences between the countries.

The findings show that non-pharmaceutical interventions caused a significant disruption in RSV seasonality during the COVID-19 pandemic, followed by an atypical rebound and early peak after the relaxation of preventive measures that were obligated. The

number of RSV immunizations at VUH SK decreased over a five-year period, despite the clinical value and need of prophylaxis for vulnerable pediatric populations. Meanwhile, countries such as Germany have introduced the availability to use a different monoclonal antibody injection, such as nirsevimab, displaying increased protection for the infants.

The study suggests that, whereas Lithuania presently relies on injections with palivizumab for RSV immunoprophylaxis, introducing advanced techniques may improve the baby's protection. Raising awareness, offering parental education and motivation are crucial to reach the goal of elevating the rates of immunization and thereby ensure safety from RSV-related medical complications in the small child.

Keywords: Respiratory syncytial virus; bronchiolitis; infants; prevention; palivizumab; nirsevimab

1. INTRODUCTION

Respiratory syncytial virus (RSV) is known to be one of the most common pathogens that causes acute lower respiratory infections such as bronchiolitis and pneumonia in neonates and infants, making it one of the biggest global health challenges in pediatric and neonatology centers. The degree of illness varies greatly, ranging from asymptomatic to mild upper respiratory infection to lower respiratory tract infections, which includes bronchiolitis and pneumonia and sometimes results in death (1).

The rate of morbidity and mortality, especially in resource-poor countries, is high (2). In resource-abundant countries, most pediatric RSV deaths occur in preterm infants and those with comorbid pathology. RSV infections occur at least once in the first two years of life in up to 90% of children (3). The explanation could be that in neonates and infants, their immune systems are immature, the airways are still relatively small, and there are only a few protective maternal antibodies present. There will always be the possibility of RSV infection being critical in this age group, so it may require hospitalization with intensive care measurements in cases when complications occur.

Despite the medical advances, RSV continues to be a burden with seasonal outbreaks, making health care systems all over the world go through strain. In addition to acute symptoms during the infection, accumulating data suggests that experiencing a respiratory syncytial virus infection in early years of life may be associated with an elevated risk of long-term respiratory disorders, including recurrent wheeze, asthma, reduced lung function, and potentially premature adult death from respiratory disease (4).

It is important to realize the epidemiology, clinical presentation, and factors that predispose to RSV in neonates and small infants for an effective implementation of prevention and treatment strategies to improve the impact of respiratory syncytial viral infection in the future all over the world.

1.1 RESEARCH AIM

This study aims to review the scientific literature on neonatal and infant RSV infection, changes in the seasonality of RSV infection, and to analyze the practice of RSV immunoprophylaxis in Lithuania and abroad.

1.2 RESEARCH OBJECTIVES

The following research objectives are developed:

1. To review the scientific literature on the prevalence, seasonality, clinical course, diagnostics, treatment recommendations, and prevention of RSV infection in newborns and infants.
2. To evaluate the changes in the number of patients treated for RSV infection in the Neonatal Centre of Vilnius University Hospital Santaros Klinikos (VUH SK) before and after the Covid-19 pandemic and to compare the data obtained with the seasonality of RSV infection in other countries of the northern hemisphere.
3. Overview of infant and children RSV immunoprophylaxis at VUH SK during 2020 - 2025.
4. Overview of RSV immunization practice in Germany.

2. METHODS

2.1 ELIGIBILITY CRITERIA

The applied inclusion criteria for the literature review were as follows:
Published studies from peer-reviewed journals.
Studies published in the English and German language.
Studies published between 2020 and 2025.

Articles and studies with data on the epidemiology, clinical manifestations, risk factors, treatment, and prevention of RSV, as well as searching for diseases secondary to RSV infection such as bronchiolitis and its impact on healthcare in pediatric patients.

The applied exclusion criteria for the literature review were as follows:
Studies that are not on RSV- related clinical pictures.
Articles that are not related to other age groups like adults or the elderly.
Publications that are not written in the English or German language.
Studies that were published before the year 2020.

2.2 INFORMATION SOURCES AND SEARCH

An electronic search was conducted via PubMed, ResearchGate and UpToDate databases with articles published between the year of 2020 and 2025, limited to English or German language and free full texts availability. Published papers based on the thesis topic were found and chosen based on the following keywords: (Respiratory Syncytial Virus) (RSV) (Neonates) (Infants) (Lower respiratory infections) (Preterm infants) (Antiviral therapies) (Pregnancy) (Prevention) (Bronchiolitis) (Seasonality) (Route of transmission) (Covid-19) (Vaccination) (Northern hemisphere). Boolean operators (AND, OR NOT) were used to assure that the search results are enhanced, and all the literature is reviewed accordingly.

3. LITERATURE REVIEW

3.1 ETIOLOGY AND RISK FACTORS

The respiratory syncytial virus has a specific structure (figure 1) which is important to understand before going into detail about the course of the infection in neonates and infants. The virus is a single stranded, negative strand RNA virus. It belongs to the *Orthopneumovirus* genus, which is part of the *Pneumoviridae* family (1). RSV's structure is that of a bilipid-

layer-envelope surrounding a ribonucleoprotein core, with many membrane proteins, one of those proteins functions in the attachment to host cells, the so-called Glycoprotein G and the other in fusing to host cells which is named the RSV fusion (F) protein. There are two antigenic subtypes of the virus, they are divided into subtype A and B (5) . Continuing, with the epidemiological characteristics of respiratory syncytial virus, RSV tends to increase the risk for recurrent infections, mainly due to its viral proteins ability to act as immune modulators by altering the normal host immune response. This property allows the virus to escape from being memorized by the immune system, hence promoting reinfection, even in already exposed individuals. In addition, a high number of children are noted to get infected with the viral pathogen within the first 5 years of life and present with the typical lower respiratory tract infection symptoms (6).

RSV causes acute respiratory disease in people of all ages. Clinical presentation depends on age, health status and whether the infection is primary or secondary.
In neonates and infants, the most common clinical manifestation of RSV infection is lower respiratory tract infection (i.e., bronchiolitis). Patients who belong to the group who are prone to experience severe illness, complications or even death due to an infection with the viral pathogen, are noted to be premature newborns, patients with prior cardiac, pulmonary, neurologic, and immunologic diseases (5). Besides the beforementioned groups, individuals with genetic disorders like Down syndrome have a high probability to develop complications as well as older patients who are frail and live in longtime facilities (7). Environmental factors like air pollution, active and/ or passive smoking as well as overcrowded closed places contribute to a higher risk of getting infected (7). Moreover, RSV illness tends to be more severe in male infants, primarily because their airways have a smaller diameter compared to female infants (7).

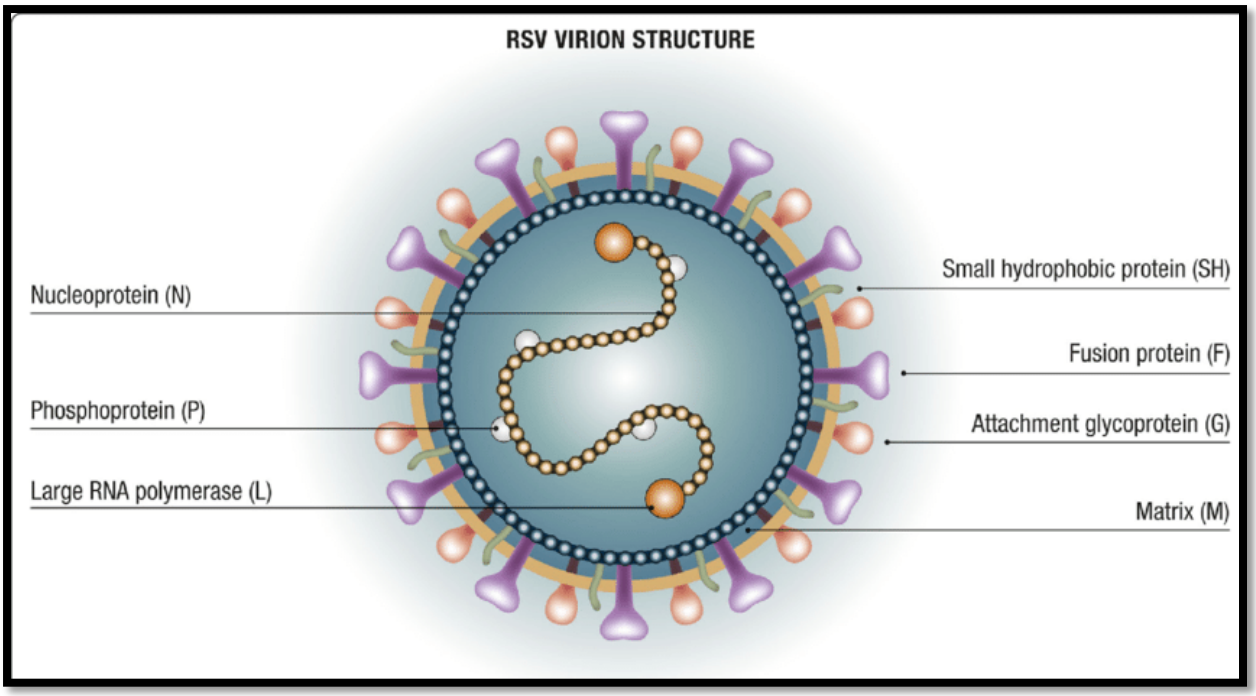

Figure 1. Structure of the Respiratory Syncytial Virus (8)

3.2 EPIDEMIOLOGY AND ROUTES OF TRANSMISSION

RSV is a global issue affecting about 3.2 million children under the age of 5 years worldwide, who end up at the hospital due to the need of medical intervention which require prolonged hospital stay (9). In this context, the need of preventive strategies must be stressed and ideally be available for all neonates and infants to improve global health outcomes. A systemic review on the epidemiological burden of RSV in Germany evaluates that RSV has been found to be a leading cause of acute lower respiratory infections (ALRI) in neonates, infants and the group of the elderly (10). RSV detection rates varied among different populations compared in this study, ranging from 5.2% to 55.4% in hospitalized children and 2.9% to 14% in adult inpatient settings (10). Additionally, they wrote that the intensive care unit (ICU) admissions and general hospitalization consequently to RSV infection in infants ranged from 3.6% to 45%, with preterm birth, congenital heart disease as well as

bronchopulmonary dysplasia (BPD) as high-risk factors for developing severe and complicated illness (10).

Another important aspect concerning the analysis of RSV infections is seasonality. The rates of infection vary extremely depending on the seasons. During the research it was found that incidence numbers differ by geography. The virus is activated more frequently at certain times of the year and dominates children's immune systems during those times. In northern hemispheres the virus peaks around December, January and February. Different situation with the southern hemispheres where the RSV cases rise between the warm months most commonly starting from June and lasting up to till September (11). During the Covid-19 pandemic, mitigation techniques like mask use, social separation, and temporary school closures were linked to a significant decrease in RSV infections in children (12,13).

To prevent high numbers of infection in the high-risk seasons it must be understood how the virus spreads. Direct contact (physical touch) is the most common route of transmission, but large droplet aerosols also have been identified to be a potential way to transmit viral material (14).

One study shows that the virus survival time varies depending on different types of surfaces with different material (figure 2), overall, the longest time for the virus to survive is up to 6 hours on nonporous surfaces as on the other hand the shortest time of survival of RSV is up to 30 minutes on skin (14). After the virus is inoculated within the mucous membranes the incubation period lasts 2-8 days. The process of viral shedding takes place approximately from 3-8 days and can be prolonged up to >3 weeks in infants and immunocompromised patients. For these reasons, enough attention must be paid to hygiene and preventative measures during RSV outbreaks, especially in high-risk facilities such as hospitals, kindergartens and schools.

Generally, it is said that common respiratory viruses such as the influenza virus and the respiratory syncytial virus have been shown to easily cross the placental barrier and spread in hematogenous pathways from the respiratory tract of a pregnant woman to the developing fetus (15). Trinh et al. (2023) compared the incidence of vertical transmission of RSV and SARS-CoV-2 infection in pregnant women and the results are proving (15). According to the article, RSV was transmitted from mother to fetus in 25.2% of the instances analyzed (15). The study additionally discovered that RSV- exposed fetuses had considerable immune-

inflammatory responses, as seen by increased cytokine synthesis, which could impact fetal development and immunological control, Trinh et al. (2023) states that RSV can affect fetal growth, resulting in lower birth weights and potential long-term health problems (15). Importantly, vertical transmission of RSV appeared to be more common than that of SARS-CoV-2 in the examined cohort, emphasizing the risk of RSV during pregnancy (15).

Finally, due to the easy spread of RSV, its seasonal occurrence and its ability to transmit vertically during pregnancy, more awareness about RSV propagation must be recognized.

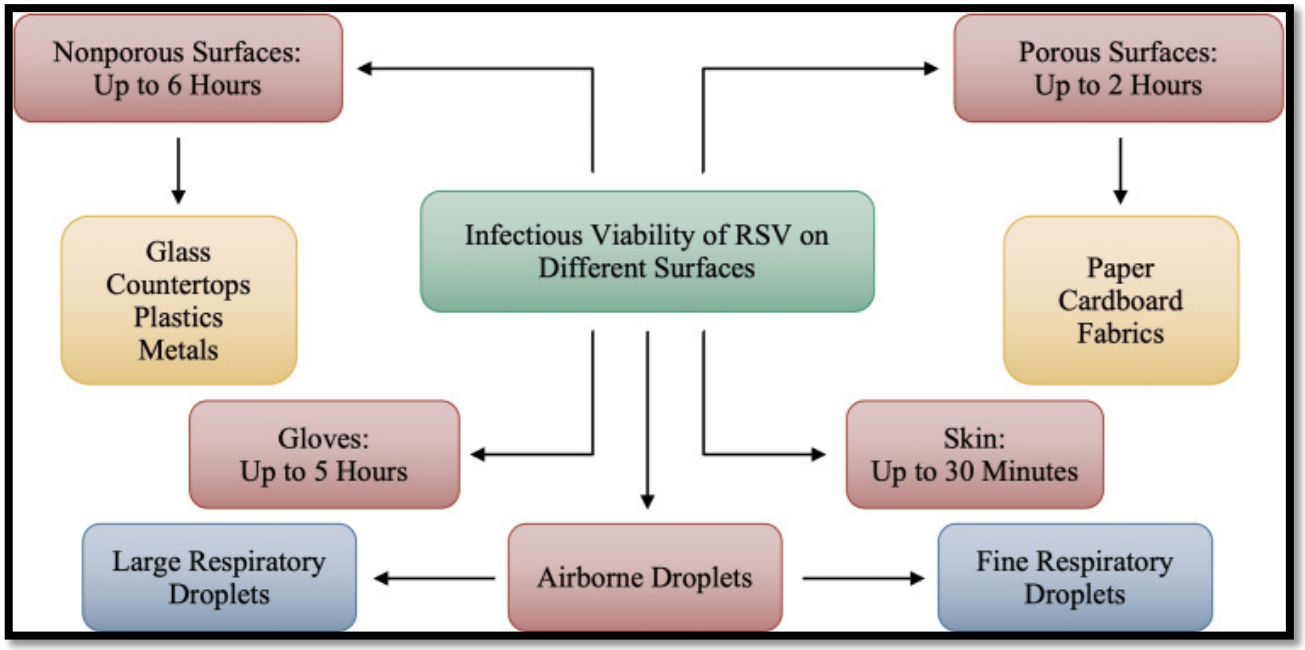

Figure 2. Infectious Viability of RSV on different surfaces (14)

3.3 CLINICAL MANIFESTATION

Signs and symptoms of RSV infection can differ and depend on several factors e.g. risk factors, age and comorbidities. As already mentioned before, neonates and infants (< 1 year of age) or premature babies are prone to suffer from severe courses of the disease accompanied by complications or even sudden infant death (16). Nevertheless, RSV infection

is possible at any age. Children who are infected with the virus for the first time, especially if they are exposed to infancy, are most at risk of experiencing severe symptoms. By the time a child reaches the age of three years, almost everyone has contracted RSV, and reinfection occurs frequently after that. Respiratory syncytial virus infections are frequent in children over the age of two, although at this age they usually present as flu-like sickness; severe breathing problems caused by RSV are rare in children over the age of two, unless they also have other comorbidities, including e.g. asthma (17). Different populations express different clinical pictures. If infection occurs in the age group younger than 2 years, it is described as an infection in infants and young children, in such cases it typically manifests with symptoms affecting the lower respiratory tract (LRT). The most common complaints result from bronchiolitis. The pathogenesis of bronchiolitis is understood as an inflammation of the bronchioles caused by viral pathogens (figure 3). This inflammation results in a blockage, which can be either partially or total of the airways and thus the physical examination reveals findings such as wheezing. Patients with the diagnosis of bronchiolitis present with an onset of symptoms for about 1-3 days. These signs include rhinorrhea, nasal congestion, sore throat, fever, decreased appetite and mild cough. This set of complaints are initiating symptoms affecting the upper respiratory tract (URTIs) which will transform into a collection of manifestation characteristics for lower respiratory tract infections (LRTIs) (17). When observing the infant or small child tachypnea, wheezing, and/ or coughing may be seen. The cough can be longstanding and lasts up to 2 weeks or more (17). Moreover, children suffering from this stage of the disease may present with signs of dehydration (decreased skin turgor, pale mucous membranes, xerostomia, absence of crying or dry diapers etc.) this results from difficulties in feeding the infant, because nasal congestion and the increased breathing rate complicate the food intake. Especially in the smaller children the physical appearance of the child can give fast hints of how severe the health status is. The pediatric assessment triangle (figure 4) is an efficient tool used in pediatrics to evaluate the patient's well-being and its severity without touching the patient, therefore using such strategy is crucial in detecting acute respiratory failure in the centers of pediatrics and neonatology.

The clinical picture of RSV infection comes along with more signs and symptoms, also those that are not from pulmonary origin – they are called the extrapulmonary manifestations. These are rare and only seen in those children who suffer from severe courses

of the disease or have a known impairment of their immune system. The extrapulmonary organ systems who are involved are cardiovascular system, neurologic impairment, hepatic injury and endocrine dysfunctions (17). In infants, who are younger than the age of 3 months episodes of bradycardia was observed and are defined as secondary symptoms to the child's dreadful respiratory failure (17). Neurologic complications are noted to be extremely rare (<1%) but were expressed as seizures and cases of encephalopathy (17). Patients who are admitted to the hospital and are even on artificial breathing techniques show an increase of liver enzymes in the blood tests, nevertheless, the transaminases are only slightly elevated and only in rare cases is the liver involved and its function impaired (17). Lastly, it might happen that the child has fluid retention and electrolyte imbalances, particularly with natrium, due to deficits in the secretion of the antidiuretic hormone (ADH) there is possible evidence of hyponatremia in the child's blood (17).

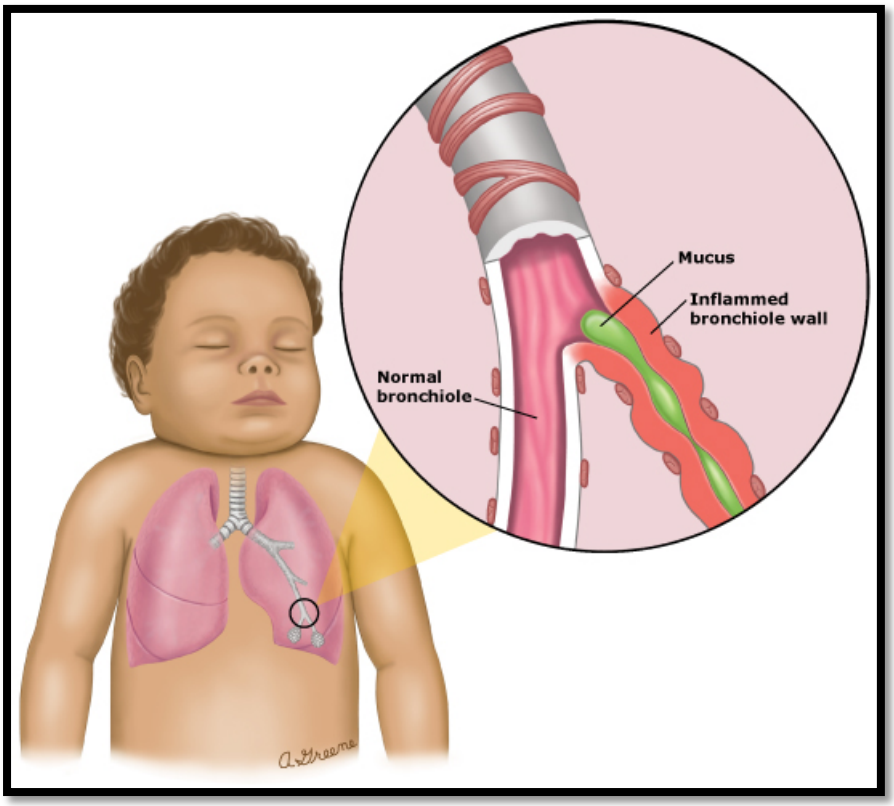

Figure 3. Inflammation of the smaller airways (bronchioles) (18)

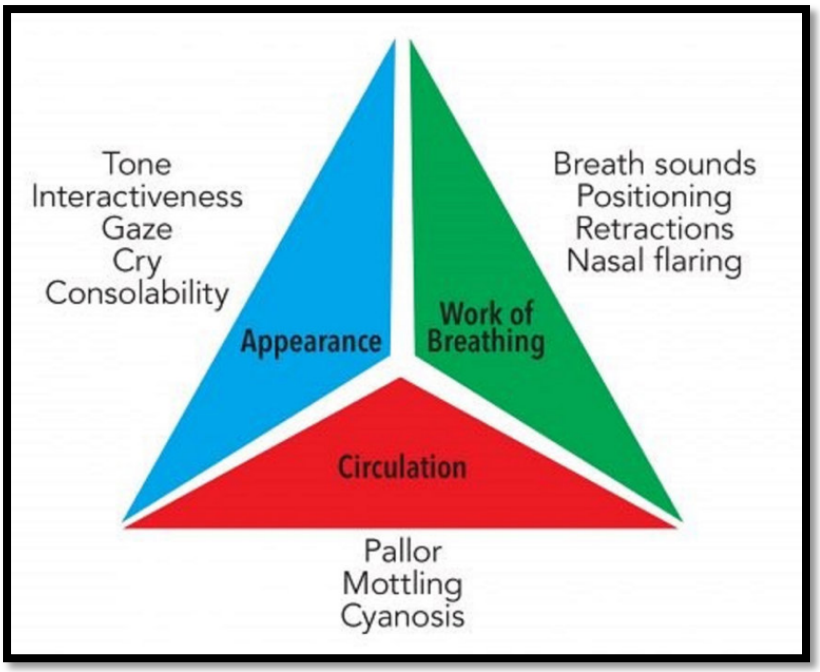

Figure 4. Pediatric Assessment Triangle (19)

It might happen that the RSV infection leads to an aggressive course of the disease in which hospitalization is needed. If the patient develops breathing abnormalities like retractions, nasal flaring, grunting, extreme tachypnea (>80 breaths per minute) or a pause of breathing for approximately 15-20 seconds as well as a bluish discoloration of the skin (cyanosis) at areas such as lips, finger and toenails, tongue or on mucous membranes for example in the mouth of the child, the patient must immediately seek medical attention. Regarding apnea associated with RSV infection, it is said to be the first sign of bronchiolitis in very young infants, which means that they are younger than 2 months of age. Additionally, this is also seen in premature born babies, those who were born before the 37th week of gestation (17).

To sum up, the key is to detect a possible RSV infection based on typical clinical features as early as possible and maintain the patient's stable health condition, to prevent life-threating complications.

3.4 DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of bronchiolitis is made based on thorough history taking and physical examination. The use of radiologic diagnostic procedures or laboratory tests are not always necessary but must be performed if the patient is in a critical status and other conditions must be ruled out e.g. pneumonia (17). When making a clinical diagnosis it is crucial not to forget about other possible reasons why the child is coming to the emergency department (ED) with the symptoms listed above, a detailed history taking is essential for not only making the accurate diagnosis but also to establish differential diagnosis's like asthma, pertussis, croup or as stated before pneumonia.

In hospitalized children, immunocompromised patients, or situations where the laboratory workup and/or instrumental findings results could affect clinical management, laboratory confirmation of RSV is usually sought (20). The polymerase chain reaction (PCR) is the recommended technique because it has great sensitivity, quick turnaround, and is immune to passive RSV antibodies (20). When used in multiplex respiratory virus panels, PCR is very helpful. Zhang et al. (2023) reports that using qRT-PCR as a diagnostic tool is a highly effective technique due to its accuracy with sensitivity ranging from 86.4% to 100% and specificity between 97.7% to 100% (21). Faster but less sensitive are rapid antigen detection tests (RADTs). Although nasopharyngeal or midturbinate swabs are frequently employed, nasal wash produces the finest specimen (20). There is the option to use tracheal aspirates or bronchoalveolar lavage in patients on ventilators or those who are undergoing bronchoscopy. Despite being conclusive, viral culture is another tool to diagnose RSV, yet it is rarely performed because of its lengthy process (20). It is important to consider a differential diagnosis for each child since RSV infection may overlap with other pathogens from the respiratory tract. To detect and therefore differentiate between various pathogens microbiological testing is helpful. In babies and youngsters, bronchiolitis caused by RSV must be differentiated from infections that originate from parainfluenza virus, metapneumovirus, influenza virus, rhinovirus, coronavirus, adenovirus, and human bocavirus (20). In extreme severe cases, coinfection with atypical pathogens which include Bordetella pertussis and Mycoplasma pneumoniae, or secondary bacterial pneumonia need to be

considered (20). A graphical overview of different viruses helps to overview the possible causative agents for acute bronchiolitis (Figure 5). RSV-associated breathing difficulties can mimic bronchial allergies exacerbations or reactive airway disease, especially when triggered by rhinovirus (20). In immunocompromised patients, viruses such as influenza, parainfluenza, cytomegalovirus (CMV), or opportunistic infections including fungal and parasitic pathogens may express signs and symptoms of the lower respiratory tract (20). To sum up, RSV is essentially a clinical diagnosis based on age, seasonality, and a pattern of characteristic respiratory symptoms, but laboratory and instrumental testing —ideally with PCR—is warranted in hospitalized or high-risk patients, where distinguishing between RSV and other viral or bacterial pathogens may be needed for proper treatment adjustments.

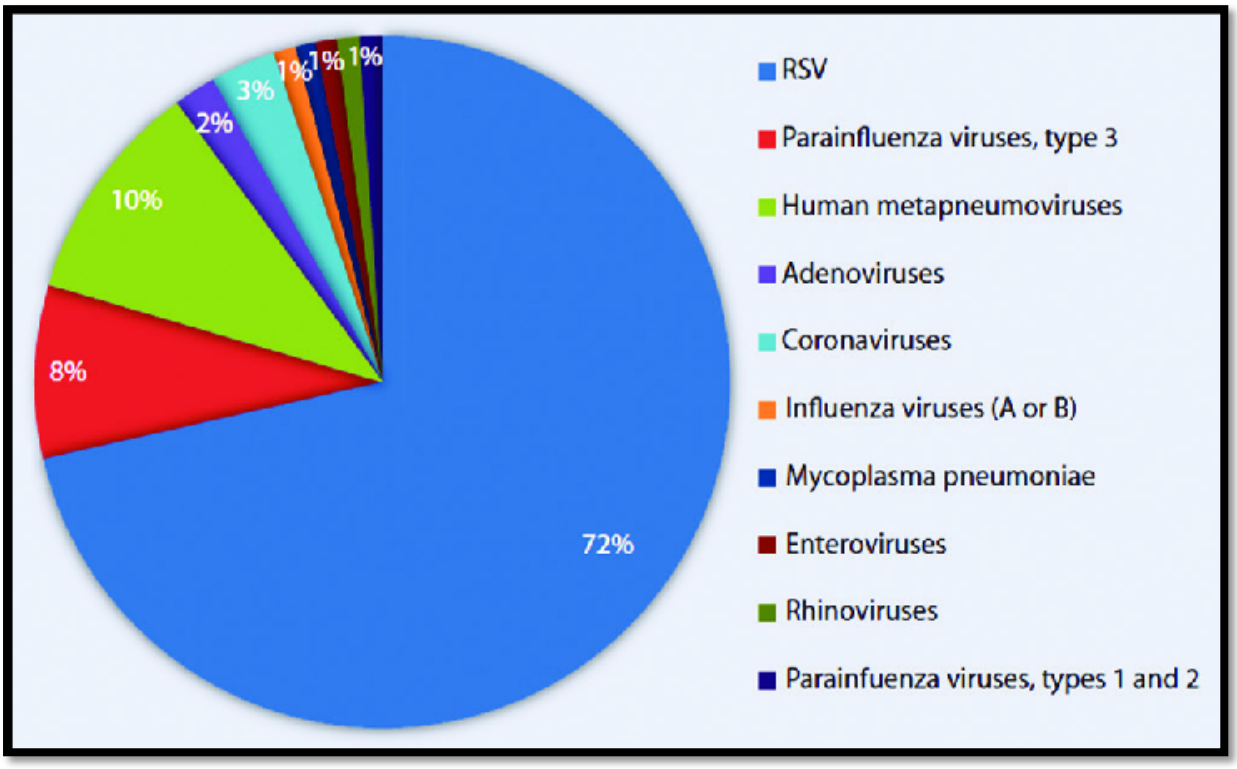

Figure 5. Causative agents of acute bronchiolitis in infancy (22).

3.5 TREATMENT STRATEGIES

The clinical management of RSV infection is multimodal, with the different treatments being applied to target the virus and supportive care to alleviate symptoms. The aims of supportive care are to alleviate symptoms and ensure adequate hydration and oxygenation for the ill child. Major components of this approach include assessing hydration status and maintaining adequate fluid intake orally or intravenously when necessary. Oxygen supplementation is extremely important for hypoxemic children and may be given through nasal cannula or high-flow oxygen therapy. In the most severe disease, with respiratory distress or apnea hospitalization is needed and respiratory support via mechanical ventilation is necessary. According to current evidence, fewer than 5% of hospitalized children require intensive respiratory support, although this rate increases among those with comorbid conditions such as prematurity, congenital heart disease, or immunodeficiency (23).

In the case of a complicated infection with lower respiratory tract involvement (i.e. bronchiolitis) the treatment tactics are like those for RSV infection and thus are directed toward the relief of symptoms and are therefore again most likely only supportive measures. Nasal congestion can be treated with saline nasal drops and suctioning (7), antipyretics such as acetaminophen or ibuprofen help to deal with fever and discomfort. Antibiotic therapy is not effective unless there is a secondary bacterial infection. Other effective measures include maternal education about preventive measures, such as hand hygiene and avoidance of infected contacts (24).

Pharmacologic therapy plays a limited role in RSV management and is typically considered for specific populations. Ribavirin, a nucleoside analog, has in vitro activity against RSV; however, it is not routinely recommended because limited clinical evidence exists for its effectiveness and it is expensive, with potential side effects such as possible intoxication and bone marrow suppression. It should be reserved for severe infections, for example in the immunocompromised patient. Manothummetha et al. (2023) declares that Ribavirin was found to be a useful treatment regimen for children with a diagnosis of hematologic malignancy (HM) or those who received hematopoietic stem cells (25). The study evaluates the efficacy of the antiviral treatment via systemic review and meta-analysis and found that in 1125 RSV-infected patients with HM/HSCT, receiving ribavirin therapy

was related with decreased mortality amongst patients with HM/HSCT suffering from symptoms of LRTI. The use of aerosolized ribavirin was linked with lower rates of progression to LRTI (25). Supportive therapy is the cornerstone of RSV management and encompasses several aspects. The main message about treatment strategies is simply that there is no treatment for RSV infection in neonates and infants, the only adequate way is to treat underlying symptoms supportively, decrease duration of illness, ensure future preventive measures to prevent further transmission of the viral material (26) and of course to ensure that the child receives emergency medical care as the disease gets worse.

3.6. PROGNOSIS

Usually the prognosis is satisfying, the illness lasts about 7-10 days, the baby may get agitated and stop eating throughout this time. However, if they are well hydrated, most babies recover in 14 to 21 days (27). As with other illnesses, an RSV infection can result in complications. In the scenario of an admitted infant there is a risk of getting co-infected (nosocomial infection) or experiencing a barotrauma as a response to mechanical ventilation (27). Bronchiolitis in infancy is associated with other diseases affecting the respiratory tract in their childhood period and is classified as a complication as well. There is a link between bronchiolitis in infancy and the development of asthma later in life. Infants who are hospitalized for bronchiolitis are three to four times more likely to develop asthma or recurrent wheeze within the first ten years of life than those who do not have bronchiolitis (17). However, it is unknown if bronchiolitis is the direct cause of asthma. Another population are those patients who have immunocompromising conditions. They are at an absolute high risk for getting infected with RSV- associated pneumonia and have a higher risk for a fatal course of the disease. To demonstrate this statement in numbers, the article provided by UpToDate gives an example that says that patients who received hematopoietic stem cell transplantation (HSCT) had a mortality rate of 70% to 100% (17). Concluding, most healthy infants recover fast and do not suffer any complications from RSV infection, on the other hand, those with weak immune systems or comorbidities struggle with severe courses of infection and even symptoms that may require intense medical attention.

3.7 PREVENTIVE STRATEGIES

Non-specific and specific protective measures can be used to prevent RSV infection. When discussing the specific preventive strategies for RSV infection it is meant to categorize between the vaccine (Abrysvo) and the monoclonal antibodies (palivizumab, nirsevimab).

3.7.1 GENERAL MEASURES

To prevent infectious diseases that may lead to a healthcare burden there are general measures that are applicable for everyone. In this chapter it is emphasized why these measures are even more important for specific groups of patients.

Three major groups are affected by the possible risk of developing a heavy course of infection including several complications. The first group are children who are at a higher risk due to their young age or present comorbidities. The Second group is those of the pregnant women and lastly the people that are aged 60 or more. As explained before the virus spreads through direct contact with fluids and objects contaminated with the viral material, therefore the inoculation of the virus in ocular and/or nasopharyngeal mucous membrane must be avoided. Easy ways to do so are proper hand washing techniques and to follow cough protection rules like covering the mouth and nose with the elbow or paper tissue. The child must be in a safe environment, that means if the child attends any public institution and has signs and symptoms of RSV infection it is advised to stay home to protect other children from becoming infected. A high-risk infant is better to isolate from public institutions during RSV season (28).

Special preventive measures are recommended for health care facilities. The Centers for Disease Control and prevention advises routine and contact precautions in inpatient and outpatient settings, such as hand sanitation, wearing gloves, surgical masks, eye protection, and disposable gowns when in contact with respiratory secretions (28). Extra measures in inpatient settings include reducing the number of people who care for both infected and uninfected patients, limiting their transport, and isolating RSV-infected patients in private rooms or housing them with other RSV-infected patients (28). Contact with high-risk patients should be avoided by visitors and medical professionals who have any upper respiratory illnesses, particularly during the height of RSV season (28).

Ultimately, active application of these preventive strategies is needed to protect those most vulnerable to RSV, especially during RSV peak season when the risk of transmission is highest.

3.7.2 IMMUNOPROPHYLAXIS

Palivizumab was the primary monoclonal antibody (mAb) used for RSV prevention before nirsevimab, particularly in high-risk newborns and special risk patients, passive immunization with the humanized antibody Palivizumab may be considered. It is approved for prophylaxis in premature infants born before the 35th week of pregnancy and in bronchopulmonary dysplasia in infants and young children up to the end of the second year of life (29). Palivizumab travels throughout the body to all organ systems after being administered intramuscularly, including the lower respiratory tract. In the event of exposure, it binds to RSV's F-protein, both before and after fusion, and prevents the conformational change required for the virus to fuse to the respiratory epithelia. Without this fusion, the virus is unable to enter the cell and then proliferate. Palivizumab can also inhibit RSV-infected cells from fusing together.

The World Health Organization (WHO) suggested introducing the new monoclonal antibodies to the regular immunization schedule to provide a global public health milestone in the disease control of severe RSV infections in children (30). There are some differences in palivizumab administration tactics in different countries. For example, in Lithuania the following children are selected for free palivizumab immunoprophylaxis:
≤ 28 weeks gestational age (GA) newborns less than 12 months old at the start of the RSV infection season; those born with a GA of 29-30 weeks and newborns less than 6 months old at the start of the RSV infection season. Moreover, infants and children diagnosed with bronchopulmonary dysplasia (BPD) under 2 years of age at the start of the RSV infection season and infants and children diagnosed with a hemodynamically significant congenital heart disease under 2 years of age at the start of the RSV infection season are considered for free immunization as well. Other neonates and infants are selected on a consensual basis if they have risk factors that may complicate the clinical course of RSV infection.

The administration of palivizumab should begin at the start of the RSV season, typically from mid-October, with four additional doses given at four-week intervals. There are limitations in its use, especially for children over two years and those with mild heart defects or other conditions like cystic fibrosis, where its efficacy is not strongly supported (29). Palivizumab is not recommended for preventing nosocomial RSV infections or treating active RSV infections. Additionally, it may be recommended for other individuals, such as those with lung anomalies or neuromuscular disorders. The advised dose is 15 mg/kg monthly, with a maximum of five doses during the RSV season. The first dose should be given before the RSV season begins (29). According to a systemic review and meta-analysis, El-Atawi et al. (2023) declares that the use of this mAb should be used cautiously, considering the high cost of palivizumab and the probable side effects such as injection site reactions (31). Further studies regarding the effectiveness of palivizumab prophylaxis in reducing ICU hospitalizations, mechanical ventilation, and long-term respiratory morbidity are needed. Cost-effectiveness also needs to be studied to propose evidence-based recommendations on the best use of palivizumab for RSV immune prophylaxis in pediatric groups (31).

Nirsevimab is a monoclonal antibody, that acts on the perfusion state of RSV F glycoprotein. It was approved by the US Food and Drug Administration in 2023 for all infants and should be used in place of palivizumab, unless nirsevimab is not available (28). Nirsevimab is recommended over palivizumab due to its extended duration of action and fewer required doses. Nirsevimab is administered once at the beginning of RSV season and confers protection for over five months due to a long half-life. A single intramuscular injection with nirsevimab was effective in 79.5% and 77.3% in healthy term and pre-term born infants against medically attended RSV LRTI and RSV hospitalization for 150 days of follow-up (32). All infants under 8 months of age who are at risk of facing their first RSV season should receive nirsevimab, unless the mother received an RSV vaccine during pregnancy (28). It is also recommended for those infants with higher risk, between 8 and 19 months, to receive a dose before the second RSV season (29). The safety profile of nirsevimab is comparable to that of a placebo, with no significant increase in serious adverse events reported during clinical trials. Common adverse reactions to nirsevimab include injection site-related reactions such as pain, swelling, hardness, or redness, and rash within 7-14 days from administration. Rare adverse effects include hypersensitivity reactions, which

may be in the form of anaphylaxis, and thrombocytopenia (33). Overall, nirsevimab represents a significant advancement in RSV prevention, simplifying the process by requiring only one dose per season, making it a preferred option for protecting at-risk infants during their first RSV season (29). To conclude, factors such as RSV seasonality, costs and healthcare system organization will most likely continue to result in preferred implementation strategies that vary between countries (32). According to Hak et al. (2023) France and Spain have already adopted a seasonal mAb program for the 2023–2024 RSV season, while the UK favors a year-round program—either mAb or maternal vaccination—for logistical simplicity (32). The Centers for Disease Control and Prevention recommended seasonal use of either nirsevimab or maternal RSV vaccination without favoring one over another in the United States (32). Nirsevimab is step by step approaching the pharmaceutical and medical markets in the world. To evaluate the efficacy of it, it must be compliant with parental decisions about the immunization of the children. A prospective longitudinal cohort study in France investigated the acceptance and safety of nirsevimab in the maternity ward (34). The paper highlights the influence of parents on the progress in enhancing the RSV immunoprophylaxis with nirsevimab. The study took place at Lille University Hospital in France from September 18, 2023, to January 23, 2024. It encompassed all newborns admitted to the maternity unit whose parents consented to participate. Parents were asked whether they agreed to their baby receiving nirsevimab. Adverse events associated with the treatment were monitored by assessing any reactions of the baby two hours post-administration and again at 7-, 14-, and 30-days following discharge, based on reports from the mother. The primary objective of the research was to ascertain how many parents accepted nirsevimab for their infant. Additional factors examined included elements influencing acceptance, reasons for agreeing or declining, and the actual safety of the treatment compared to newborns who did not receive it. The hospital in France reached a high acceptance percentage of 91.6% during the first bronchiolitis season (34). Factors linked to the acceptance of nirsevimab included increased maternal age, reduced parity, and having a partner who has an enrollment in a job. There were no serious adverse events within 2 hours following the nirsevimab injection. The nirsevimab cohort and the control cohort exhibited no statistically relevant differences in the frequency of adverse events recorded in the 30 days following treatment (34). There are several potential explanations for this high acceptance, one is the caliber of prenatal education provided by

healthcare professionals, which parents notably highlighted (34). Furthermore, the public's heightened awareness of last season's severe bronchiolitis outbreak, alongside the promotion of this novel preventive treatment for RSV, may be contributing factors. Certain parents opted to accept nirsevimab due to having a relative impacted by the condition or having heard about the serious consequences of bronchiolitis in infants from friends or their circle of acquaintances (34). The robust demand for nirsevimab throughout France led to a shortage of dosages for the immunization which is at first sign negatively connotated yet promising evidence of more future participants (34). As already mentioned, there were no severe side effects documented and there the overall safety profile of nirsevimab is auspicious. Ocana de Sentuary et al. (2025) found that within the nirsevimab cohort group more frequent regurgitation was seen on the 30th day after the injection (34). It is explained that the nutritional intake can be linked to the regurgitation infant because more children in the nirsevimab cohort were breastfed than in the control cohort group (34). Overall, this study suggests a bright future for the immunoprophylaxis of children with the new step by step approaching nirsevimab. A sufficient knowledge and expertise have a high influence on a parent’s decision. More awareness about this treatment can make breaking changes in controlling RSV infection in infancy.

3.7.3 VACCINATION OF PREGNANT WOMEN

When a woman gets pregnant, the body undergoes major physiological changes. This transition of the woman’s body is challenging for all organ systems, especially the cardiovascular system, the respiratory tract and it has impact of the coagulation state (Figure 6). To avoid fetal rejection, pregnancy causes a change in the mother's immune system. During pregnancy fetal rejection is automatically avoidant. This happens because the maternal immune system is in a constant balance between defense mechanism and immune tolerance. This makes the mother more vulnerable to infections, such as the respiratory syncytial virus (35). Therefor the need for maternal vaccination during pregnancy is crucial to discuss. Maternal vaccination programs are a global promising invention to prevent health

complications in mother and fetus. The routine recommendations given by the U.S Centers for Disease Control and Prevention and by the German vaccine commission (STIKO) create an appropriate vaccination plan for pregnant women. The recommended vaccines from both programs include the Tdap, Influenza and COVID-19 vaccines (36,37). They are good examples for successful prevention of infectious diseases. In Lithuania, pregnant women can also be vaccinated with these vaccines with state budget funds.

Nevertheless, there are other diseases which need urgent progress in prevention and prophylactic strategies for a brighter future. Sadly, not enough have been established or gone through trials completely. RSV is a high burden to public health, therefore, in 2023, the European Union granted approval for the inaugural RSV vaccine aimed at safeguarding infants up to six months of age, in addition to two vaccines intended for older adults. When given to a pregnant woman, this vaccine stimulates the generation of antibodies that cross the placenta to the fetus, thereby offering protection to the offspring for a duration of up to six months following delivery (38). Even though some countries have the possibility to vaccinate pregnant women, the effectiveness of the transfer of the RSV antibodies may be disrupted by several biological factors. This issue was analyzed by one study, that focused especially on the impact on low-middle income countries (LMIC). A series of biologic factors have been found to potentially blunt with the transfer of protective naturally acquired antibodies from mother to fetus, thereby diminishing vaccine effectiveness by impeding the transfer of vaccine-induced antibodies (39). Many of these characteristics are shared by LMICs, which carry the highest burden of RSV-associated death (39). The following are possible factors declared by Atwell et al. (2022), which have impact on the transplacental transfer: preterm delivery, low birthweight, maternal HIV infection, placental malaria, and hypergammaglobulinemia (39). For babies who are born prematurely the benefit of maternal immunization is limited because antibody transfer only reaches peak levels at the end of the third trimester (32). The study aimed to express the importance of not only the development of RSV immunization in pregnancy but also to ensure the effectiveness and optimization of antibody transfer on the transplacental transmission. Continuing, there is one study that proves that the vaccination process is effective and contributes to a promising future for the RSV prevention in neonates and infants. The article presents three types of vaccine which are as follows: RSVpreF3, RSV stabilized prefusion F subunit vaccine (RSVpreF) and RSV

fusion (F) protein nanoparticle vaccines (RSV F vaccine) (40). In the following all of them will be shortly introduced and the results of the study will be summarized. The RSVpreF3 vaccine is an adjuvant-free vaccination with good immunogenicity and safety characteristics (40). Neutralizing antibodies (nAbs) increased significantly in mothers and their newborns during the trials; levels peaked at birth and then gradually decreased over the course of 181 days postpartum (40). Events that occurred were mild to moderate. Different results were seen with the RSVpreF variant. NAbs significantly increased with this vaccine, transferring from 1.4% to 2.10% via the placenta (40). With adverse event rates comparable to the placebo group, it was well-tolerated (40). Last to mention are the effects of RSV F vaccine revealed by the study. Pregnant women who received this nanoparticle vaccine showed a significant increase in RSV-specific antibody levels, with 90% to 120% of the antibodies transferred to the neonates (40). In the first ninety-day period of life, the vaccine demonstrated a 39.4% efficacy against RSV-associated lower respiratory tract infections (LRTI); no cases of severe RSV disease were observed in the neonates (40). To reach those promising health outcomes prior to maternal vaccination it is essential for the mothers to have accesses to a qualitative antenatal care. But not only the availability is important, but also the willingness of a woman to attend such appointments (41).

The last part of this chapter evaluates a study about the vaccine that is considerable for a woman who is expecting a child the so called - Abrysvo vaccine. It is a RSVpreF vaccine manufactured by Pfizer. During the gestational week 32 to 36 the intramuscular injection is made. This specific vaccine is the only approved for pregnant woman, but the elderly population (>60 years) are accepted for the usage as well (42). The mode of action of the Abrysvo vaccine is immunizing the fetus passively, therefore, the maternal antibody is transferred to the offspring during pregnancy and breastfeeding (Figure 7). RSV-specific antibodies produced upon vaccination with the vaccine neutralize the virus through inhibition of its host cellular entry mechanism (42). The safety profile of the vaccine highly depends on the timing of injection. The U.S Food and Drug administration (FDA) permitted the application of one dose of Abrysvo vaccine, containing 0.5 mL which must be administered intramuscularly, between 32 and 36 weeks of pregnancy (42). This late gestation period was the final recommendation due to evidence from the clinical investigations showing that immunization before 32 weeks may increase the rate of preterm deliveries (42). The timing of

vaccination is important because it influences the level of maternal antibody transmission to the newborn; longer intervals between immunization and birth result in larger levels of antibodies transferred.

To sum up, to make antenatal care more trending, the key is to teach, motivate and establish trust with the mother and to create a balance between the willingness of immunization and its availability.

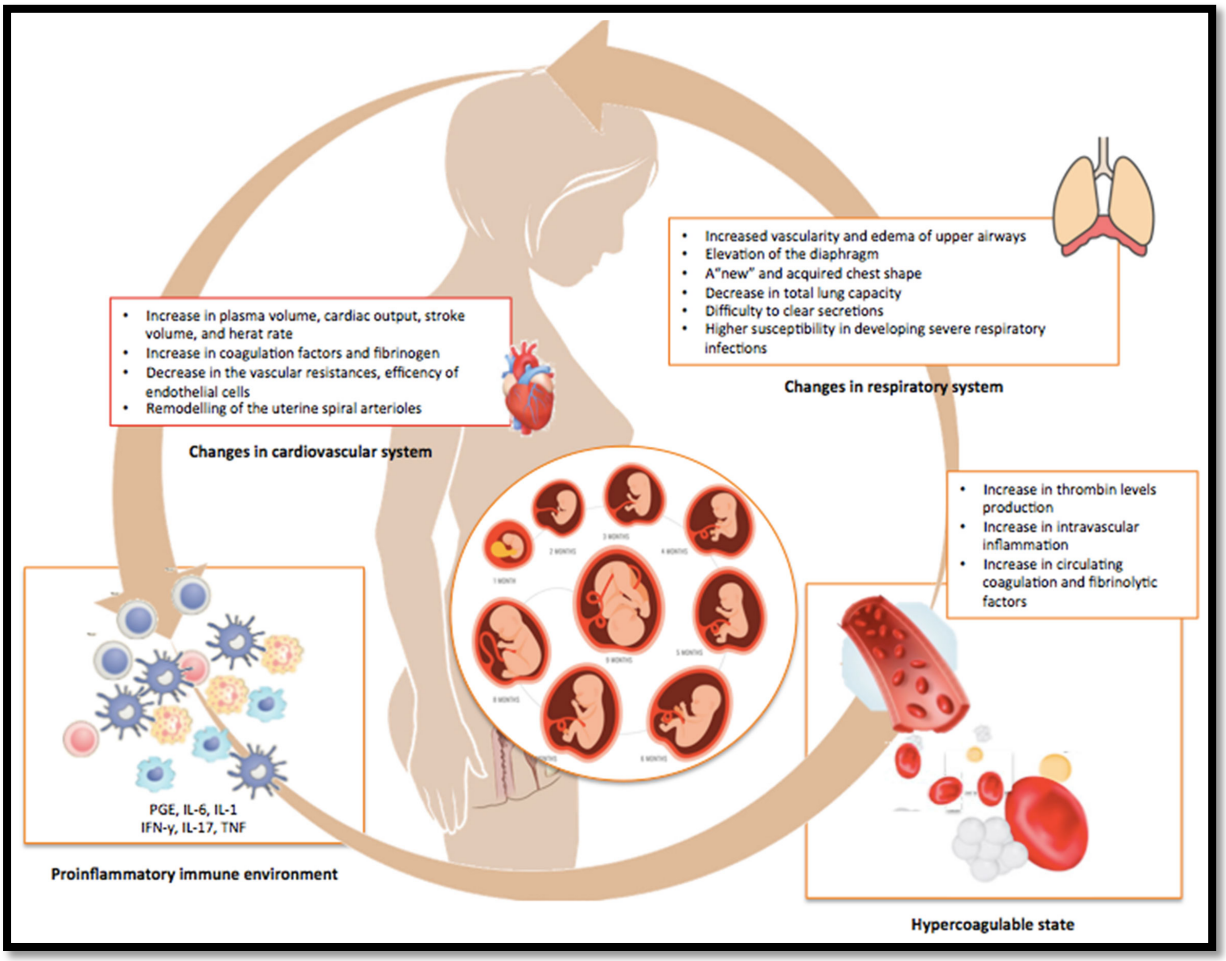

Figure 6. Physiological changes during pregnancy (35).

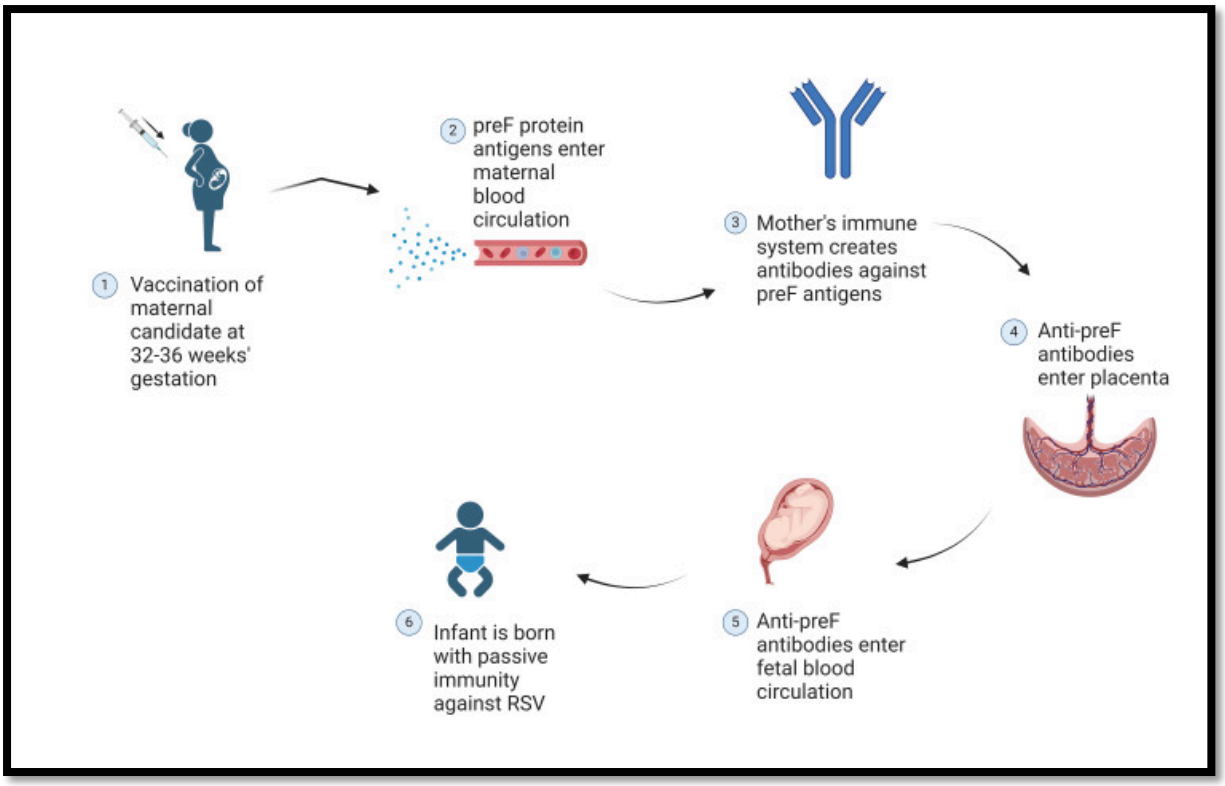

Figure 7. Scheme of maternal antibody transfer via Abrysvo (42).

4. OVERVIEW OF RSV SEASONALITY CHANGES

4.1 RSV INCIDENCE IN THE PERIOD 2019 – 2025 AT THE VUH SK NEONATOLOGY CENTER

This chapter provides an overview of the number of cases of RSV infections in the VUH SK Neonatology Centre before and after the Covid-19 pandemic. The data is presented in figure 8. The graph shows the number of patients treated for RSV in the VUH SK Neonatology Centre over multiple years, from September to May. According to the data, RSV infections exhibited a seasonal trend before the COVID-19 pandemic, with peaks occurring during the winter months. RSV infections rose sharply from December to March in the 2019–20 season, reaching a high in March, this is illustrated by the blue graph. Such an occurrence of cases demonstrates the virus's typical pattern, in which it appears and flourishes during the cold season when the environment is conducive to transmission.

However, as the flat black graph indicates, there were no detected RSV infections during the 2020–21 cold season. The extensive use of pandemic control measures may have led to the downfall or even absence of RSV infection numbers. Certain public health policies like the global use of mandatory face masks, social separation, and limiting hospital visits diminished the spread of respiratory diseases like RSV drastically. A completely new variation in seasonality was observed in RSV infections during the post-pandemic period indicated by the red graph. Infections began to rise in September and peaked unusually early in October until December during the 2021-22 season. The peak of the 2022–23 season happened even earlier, beginning in September and peaking in December, indicating that the virus's seasonal dynamics have shifted. For larger segments of the population who were not as exposed during these times, this can be explained by both decreased population immunity and increased susceptibility to illness. With infections increasing gradually from November to February in the 2023–24 season, the trend changed once more, suggesting a potential return to the pre-pandemic seasonal pattern. The most recent data from 2024-25 shows a return to the typical RSV pattern, where the cases of infection start rising from November and peaking in February and March. This suggests a return of the conventional RSV epidemiology.

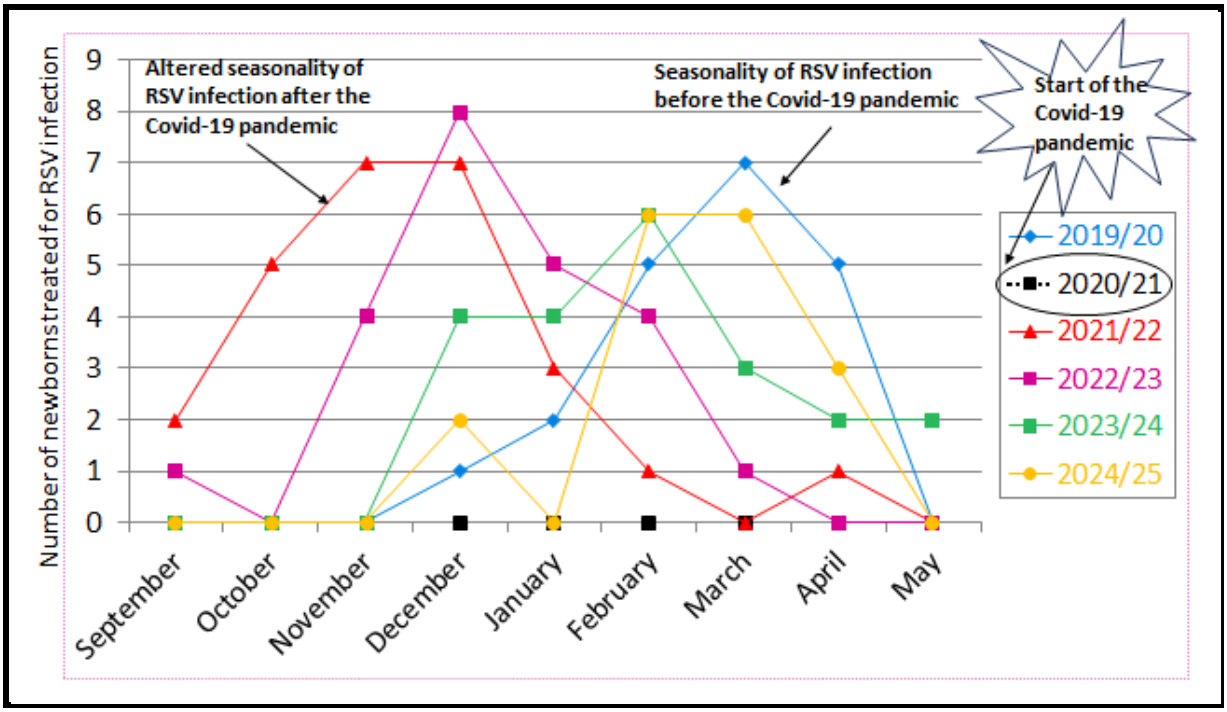

Figure 8. Paulaviciene Ieva Jura. Seasonal changes in RSV incidence (the y-axis indicates the number of patients treated for RSV infection in VUH SK Neonatal unit over several years).

4.2 COMPARISION WITH SEASONAL CHANGES IN THE U.S.

The graph in the article "Seasonality of Respiratory Syncytial Virus — United States, 2017-2023" depicts the proportion of positive RSV polymerase chain reaction (PCR) test findings in the United States over a few years (Figure 9.). Prior to the COVID-19 pandemic, RSV epidemics normally started in October, peaked in December, and ended in April. However, the typical winter RSV outbreak wasn't observed in 2020-21, most likely due to widespread use of nonpharmaceutical measures such as mask-wearing and social separation (43). In the following 2021-22 season, RSV activity began early in May, peaked at the end of July, and terminated in January. The 2022-23 season began in June, peaked in November. The numbers of positive tested cases sharply decreased from the peak in November until it ended at the end of February, indicating a return to pre-pandemic seasonality although with significant variations. Both graphs show a notable disturbance in normal RSV patterns during the pandemic, followed by a recovery to RSV activity in the post-pandemic era, when compared to the neonatal unit in Vilnius. There are several circumstances which might have contributed to this unusual outbreak of RSV after the global COVID-19 pandemic. First, the reduced travel restrictions and therefore the higher amounts of worldwide travel being available again play a major role. Secondly, the restoration of socioeconomic activities may have led to this rare endemic (44). Additionally, differences in the re-emergence of RSV depend on country to country. This may be related to national policies, notably how each country has handled COVID-19, and, particularly, how they managed to use non-pharmaceutical interventions (NPI) to control the pandemic (44).

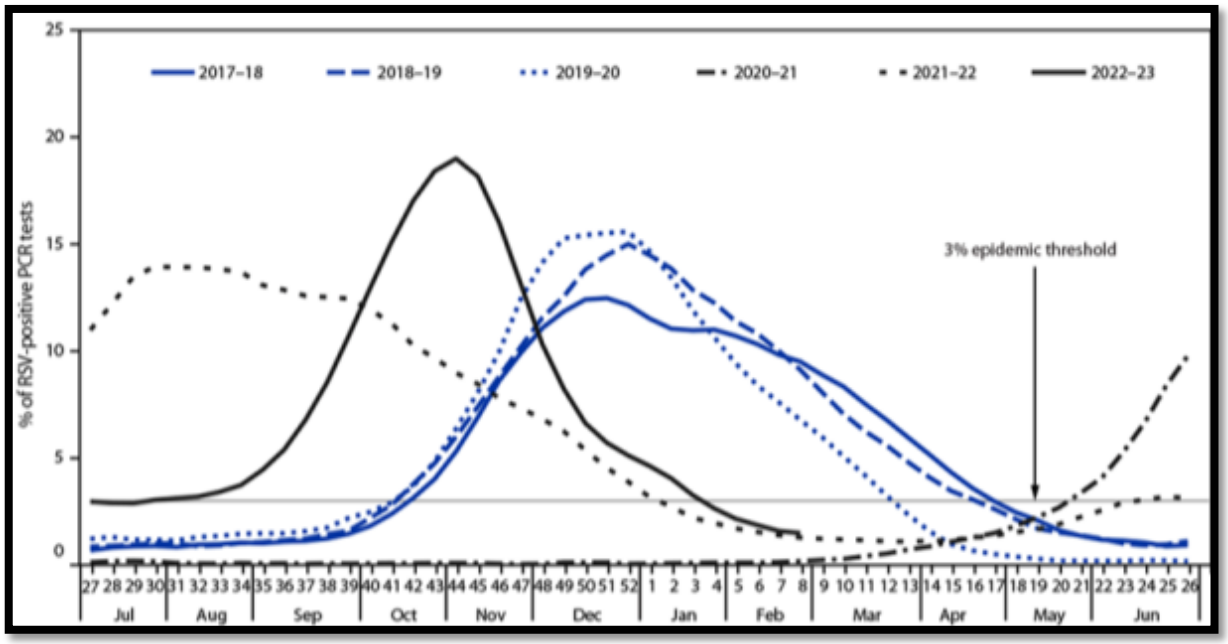

Figure 9. Hamid S, Winn A, Parikh R, et al. Seasonality of Respiratory Syncytial Virus — United States, 2017–2023. MMWR Morb Mortal Wkly Rep 2023; 72:355–361 (43)

4.3 COMPARISON WITH SEASONAL CHANGES IN ASTURIAS, NORTHERN SPAIN

The compared study was performed in Asturias, which is in the North of Spain. It shows the influence of the COVID-19 pandemic on various respiratory viruses, which have differences in their viral structure. As known from the data obtained at the neonatal unit in Vilnius, the peak of infection happened in the cold months, such as November and December and lasted typically until early spring. However, during the pandemic, NPIs including mask rules, lockdowns, and isolation from others broke the pattern. Early in the pandemic, when strict lockdown measures were implemented from March to June 2020, RSV essentially vanished in Asturias, Spain, according to García-García et al. (2022) (45). Even after limitations were loosened and schools began in September, the virus remained undetected throughout the 2020 winter season. Remarkably, RSV made a comeback in Asturias in May 2021, with an unusual summer peak in July. This observation is consistent with delayed RSV outbreaks that have been documented in other parts of Spain and other places (45). According

to research on competing viral dynamics, these changes imply that a few factors, such as decreased social contact and possible viral interference from Sars-CoV-2, may have inhibited RSV circulation. Di Mattia et al. (2021), states that the establishment of travel limitation and closure of borders might have influenced the spread of RSV across different countries (46). García-García and colleagues argue that understanding altering transmission dynamics can inform public health strategies, particularly during pandemics that disrupt regular respiratory virus cycles. Furthermore, the study demonstrates how RSV, as an encapsulated virus, is especially vulnerable to public health measures such as better hand washing and the application of disinfectant solutions. The findings are consistent with broader trends observed globally, in which RSV transmission was dramatically decreased during periods of high compliance with COVID-19 preventive efforts but recovered in unanticipated seasonal patterns once these measures were loosened.

4.4 COMPARISON WITH SEASONAL CHANGES IN NORTHERN ITALY

Continuing the comparison of seasonality of RSV in Vilnius and countries from the northern hemisphere, as well as how the pandemic changed the pattern of the virus's occurrence, a retrospective, single-center study was performed in the San Gerado Hospital which is in Monza, Italy. They focus on the changes in the emergency department (ED) admissions of infants below the age of 1 year with acute bronchiolitis. Including this study is essential, since most children must suffer from the symptoms that come with the RSV resulting bronchiolitis. The graph below (figure. 10) displays how many infants in the San Gerado Hospital were diagnosed with bronchiolitis over the course of five respiratory seasons from 2017 to 2022 at the emergency department. RSV infections had a normal seasonal rhythm prior to the COVID-19 pandemic, peaking between November and January. November sees an especially steep rise in the 2018–2019 season, suggesting that RSV transmission is highest during the colder months. Nonetheless, there is a sharp decline in bronchiolitis cases throughout the 2020–2021 season. There is hardly any typical seasonal peak. Nenna et. Al. states that viral interference phenomena play a role in the absence of RSV infected children during the pandemic in Italy (47). This means that a respiratory virus-induced superinfection can be

prevented because the second active viral pathogen impends the second viral replication by the already active innate immune system (47). RSV infections recovered in the 2021–2022 season, however the peaking timing was noticeably different. Instead of seeing a peak in the usual late-fall to winter months, cases started to rise in September and peaked early, in October and November. The results presented in the graph are like the data obtained in Vilnius, Santariskes neonatal department, the study performed in Asturias, and lastly consistent with the findings of the American study. All of them suggest the high impact of the COVID-19 pandemic, which may have led to virus alteration, less transmission opportunities, and overall improved preventive measures for various respiratory viruses. The atypical bronchiolitis peak in the post-pandemic era may be explained by a worldwide loosening and partial release of Sars-CoV-2 preventative measures like the comeback of social interactions, making global travelling possible again, along with a fading herd immunity to other viruses (48). The study states that children who were diagnosed with bronchiolitis between 2021 and 2022 were born during the active phase of the Sars-CoV-2 pandemic. During this time their immune systems were less stimulated by external agents (such as bacteria and viruses) due to all the Sars-CoV2 restrictions, where even their mothers were not exposed to infections and, as a result, did not develop antibodies (48). At the “Vittore Buzzi” Children’s Hospital in Milan between November 2021 and January 2022 another study was performed to see how the RSV behaves during certain seasons. They collected 104 samples from pediatric patients at the “Vittore Buzzi” Children's Hospital. Researchers performed RT-PCR and next-generation sequencing to identify viral subgroups and sequence whole genomes. They used maximum likelihood and Bayesian phylogenetic analysis to situate the Italian sequences in a larger European context and estimate the timing of Italian clustering. The results are as follows: from 104 positive-tested patient about 76.9% required admission to the hospital, especially those infants <3 months of age, moreover the RSV-A and the RSV-B groups were equal in their occurrence (49). Those infants with evidence of the RSV-A subunit required more medical attention in form of more oxygenation and longer duration of fluid intake via intravenous route. Lai et al. (2024) claims that the unusual RSV outbreak from 2021-2022 in Italy, was most likely caused by several introductions of viral clusters that had been circulating throughout Europe for at least a decade (49). The population dynamics research revealed that RSV transmission dropped during COVID-19 lockdowns (2020-2021) but

increased after the restrictions were restored in 2021(49). This shows similarities to other countries that had increasing number of RSV infections after the loosening of the pandemic measurements.

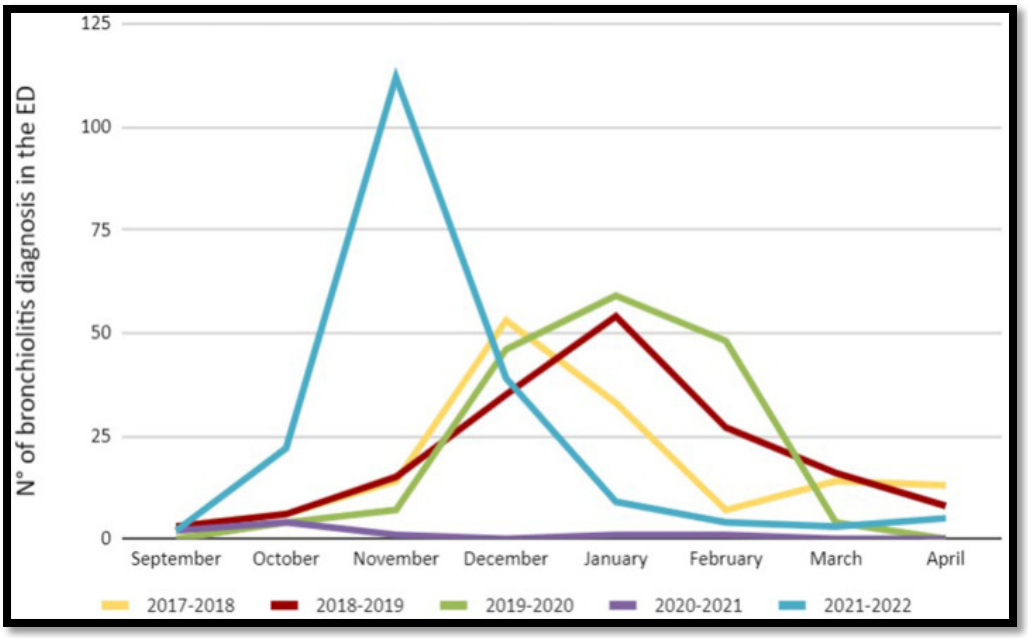

Figure. 10 Diagnosis of bronchiolitis in infants (>1Year) established in the emergency department (ED) in a Northern Italy hospital (50).

4.5 COMPARISON WITH SEASONAL CHANGES IN NORTHERN IRELAND

The following study was conducted in Northern Ireland; the authors raised some interesting and important arguments which contribute to the data obtained from Lithuania and other countries that are part of the northern hemisphere. This study examines the use of wastewater-based epidemiology (WBE) as a unique and effective tool for tracking the transmission, seasonality, and genetic development of respiratory syncytial virus (RSV), providing insights that might improve public health surveillance and outbreak preparation. Additionally, to the previous chapters about RSV epidemiology and prevention the WBE

seems to appear as quite relevant for these subcategories. WBE, which became popular during the COVID-19 pandemic, entails testing sewage to track the transmission of viruses at the community level (51). While prior research had shown that RSV could be discovered in both the liquid and solid components of wastewater (52), the goal of their research was to develop and expand that technique to then track RSV outbreaks and better understand the virus's genetic diversity. They started collecting wastewater samples weekly from 20 treatment plants across Northern Ireland (51). These samples were taken via automated devices that collected wastewater throughout the whole day to ensure complete data. Viral RNA was extracted from the samples afterwards, they underwent reverse-transcription quantitative PCR (RT-qPCR) analysis (51). By using this method, the researchers were able to determine the time and location of RSV presence in the wastewater as well as the number of RSV material found in the wastewater itself. The study discovered two big RSV epidemics over the monitoring period: one from August 2021 to January 2022, and another from July 2022 to February 2023 (51). Allen et al. draws attention to the fact that the WBE method acts as an early warning system for tracking respiratory syncytial virus outbreaks because the amount of RSV material found in the wastewater was rising even before the first clinical cases appeared in medical records, also the amount of viral products found in the water matches with high numbers of RSV detection in medical practice (51). Regarding the genetic development of the respiratory syncytial virus, Allen et al. found that both RSV subtypes (A and B) were identified by genetic research, with different strains circulating in various seasons (51). It is possible that RSV was brought to Northern Ireland from other areas because some strains were closely linked to those prevalent worldwide, despite this, other strains seemed to persist locally most likely due to weaker transmission within the population between the seasons (51). The genetic sequences of the virus were found to have mutations, some of which may affect how the virus distributes or interacts with the immune system (51).

5. OVERVIEW OF RSV IMMUNOPROPHYLAXIS IN LITHUANIA AND GERMANY

5.1 OVERVIEW OF RSV IMMUNOPROPHYLAXIS IN VUH SK IN THE PERIOD 2020-2025

An outline of VUH SK RSV immunoprophylaxis program from 2020 to 2025 is given in this chapter. Especially for susceptible groups, which were discussed previously in this paper, monoclonal antibodies are a crucial part of immunoprophylaxis, which helps to prevent serious RSV infection. This section attempts to assess the implementation and results of RSV immunoprophylaxis at VUH SK. Currently nirsevimab is not available in Lithuania, yet there is the option to treat the child according to the RSV prophylaxis recommendations. These include an intramuscular injection of palivizumab once per month for five-doses during the viral shedding season. The thesis will only discuss the number of immunized children who have concomitant diseases which classify them as a high-risk group for experiencing a severe course of the disease with RSV. There will be no data provided about reduction of mortality and effectiveness of the immunoprophylaxis.

Between 2020 – 2025 the graph (Figure 11) illustrates a downward trend of immunization of susceptible children. The consistent drop in Lithuania's birth rate can be linked to the falling number of children who have received immunization via palivizumab. The Lithuanian medical data of births noted 19797 deliveries in the year of 2023, which is 3236 fewer than in 2019. There are about 5% of preterm births in Lithuania each year, which is known to be a steady percentage over the last years (53),(54). Palivizumab injections for high-risk newborns and babies gradually declined in number. A total of 115 children received protection with the substance in 2020–2021, while the lowest number of children, 88, was attained in 2023–2024. Nonetheless, the number somewhat rose again up to 94 immunized children in 2024–2025, which is almost the same number of children that received immunoprophylaxis in the previous year (2022-2023), where 95 youngsters received immunization. Over the course of these five years, the number of newborns and infants who received palivizumab decreased by 21 individuals. Though the current year's slight increase in the number of immunized children might be the first indication of a recovery and a possible future with more immunizations applied again. Overall, the decreasing trend is still visible and must be observed over the next years.

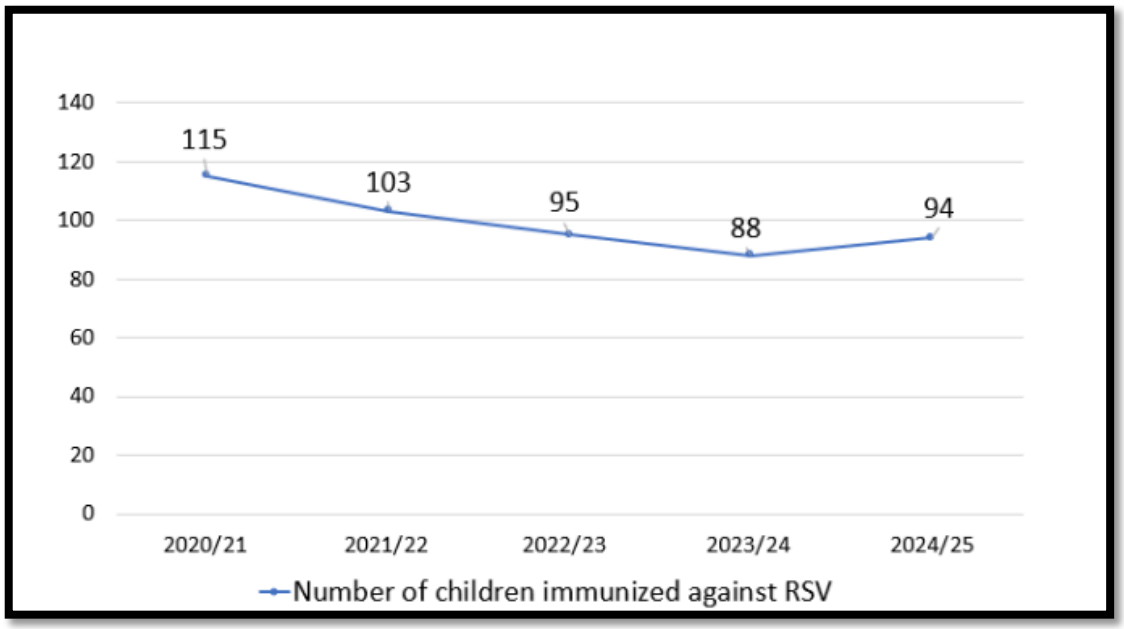

Figure. 11 Paulaviciene Ieva Jura. RSV immunization at VUH SK in 2020 – 2025

Moving on, the immunization rates vary between five different categories (Figure.12). They bear high-risk potential and may have massive impact on the course of the disease. The bar graphic below (Figure.11) demonstrates five risk groups, these are as follows: preterm infant ≤28 weeks gestational age (PTI), preterm infants 29-30 weeks GA, congenital heart disease, bronchopulmonary dysplasia >1-year-old and lastly, a category for other non-specifically mentioned reasons. The immunization rate of babies born at or before the 28th week of gestation (dark blue bar) starts high in 2020/21 and remains high over the years. After the peak in 2020/21 with 43 neonates the lowest rate with a count of 25 children was investigated in 2023/24. Hence, these results mean the demand for immunizing these patients is clinically important and gets underlined in this dark blue bar. The orange bar illustrates those individuals with congenital heart disease. These have a clinical relevance since it impacts the course of an RSV infection more often. This group presents a high and consistent scheme as well. The most patients with CHD were immunized in 2020/21with a total of 39 children and the least in 2022/23 with a value of 27 patients. Moving on to preterm infants with a GA of 29-30 weeks, their immunization level is shown by the grey bar, and it depicts that palivizumab administration was initially lower than the dark blue and orange group. It

can be noted that there is a gradual reduction over time with the least number of neonates receiving the monoclonal antibodies in the seasons of 2020/21 and 2023/24 with only 15 patients being immunized, in contrast to the peak of immunizations comprising a total of 24 immunizations in 2021/22. The children with only a diagnosis of bronchopulmonary dysplasia are presented by the yellow bar. In contrast to the beforementioned risk-groups those children got the least prophylaxis with palivizumab at VUH SK, nevertheless the dark blue and grey columns included those cases of BPD in infants < 1 year of age as well. The yellow bar illustrates one specific difference to the other bars. It is the only risk-group who reached the highest rates of immunization in the year of 2023/24 with 18 children being vaccinated in comparison to the previous years, while the others rather have declined as the years approached. The category "other "includes unspecified features, it is represented by the light blue bar. The rate of protections through immuoprophylaxis in this group ranges from 2 to 4 and is therefore consistently low across all five years.

Another bar chart was created to depict respiratory syncytial virus immunization rates at VUH SK across five immunization seasons (2020-2025). The graph splits patients into two groups: those who had a full course of palivizumab injections (5 doses) and those who received only an incomplete course, i.e. less than 5 doses during immunization season (Figure.13). The 2020/21 season had the greatest incomplete rate, with 15 children receiving an incomplete course, while they also demonstrate the highest number of 100 children who received the entire course in the same year. Both categories gradually declined in the ensuing seasons: 89 fully completed cycles vs. 14 incomplete cycles in 2021/22, and 83 completed palivizumab injections vs. 12 cycles that were interrupted in 2022/23. With 79 completed full courses and 9 incomplete courses, 2023/24 had the lowest completion rate for that cohort but on the other hand had the best results regarding the incomplete courses compared to all other years. As the most recent data reveals there is a minor rise in 2024/25, with 81 complete and 13 unfinished courses detected. The completion of an immunization course might be challenging and can lead to interruptions of the injection period. Scheduled surgeries, sanatorium treatment, infectious illnesses, parental refusal to vaccinate, emigration or vacation, and other or unidentified reasons are the primary causes of unsatisfactory immunization. To reach the maximal state of protection it is crucial that the baby is given all 5 doses via intramuscular injection during the RSV season.

Overall, even while the program shows improvement in lowering incomplete immunoprophylaxis cycles, the drop in palivizumab application rates emphasizes how vital it is to remove immunization obstacles and guarantee that all high-risk infants are completely protected against RSV.

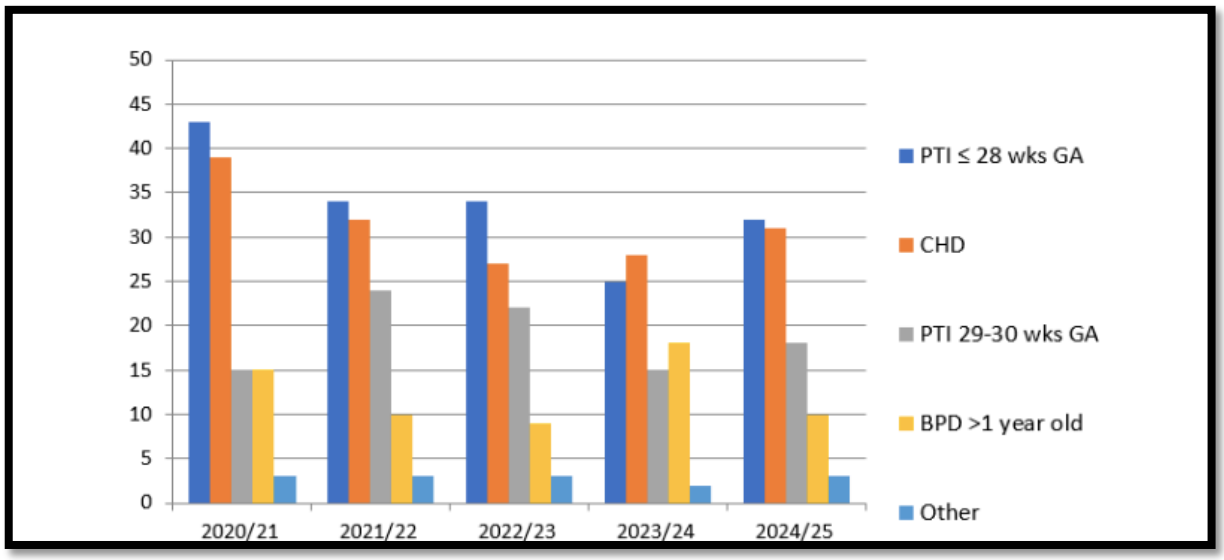

Figure 12. Paulaviciene Ieva Jura. RSV immunization according to risk groups at Vilnius University Hospital Santaros Klinikos, Children ‘s Hospital in 2020 – 2025. PTI – preterm infant, CHD – congenital heart disease (clinically significant), GA – gestational age, BPD – bronchopulmonary dysplasia.

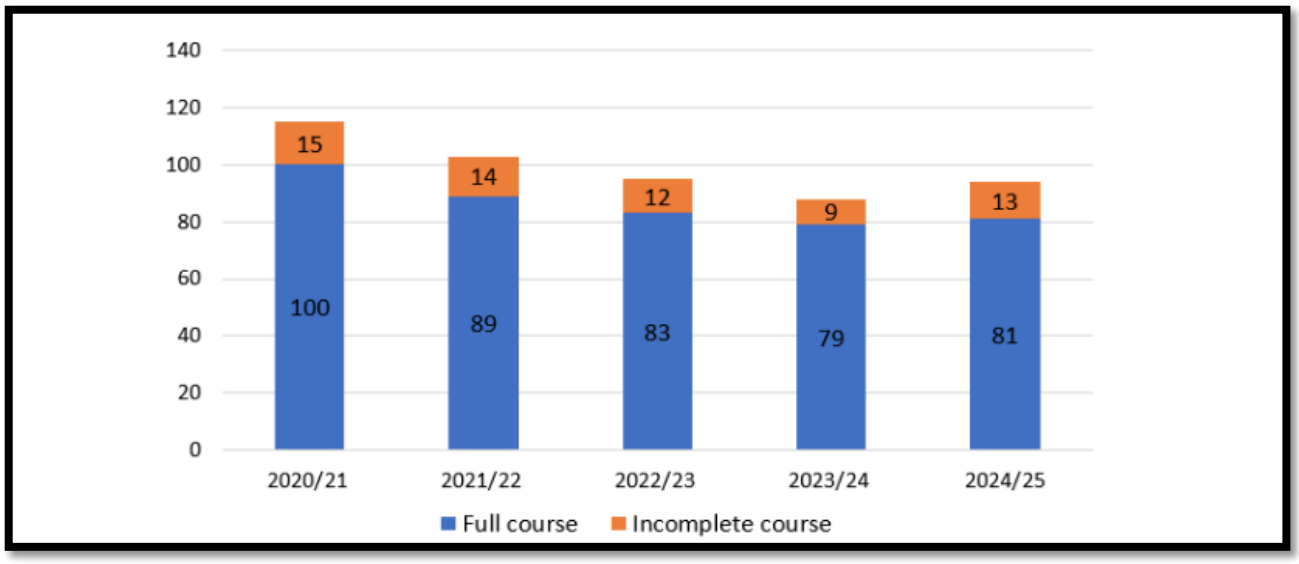

Figure 13. Paulaviciene Ieva Jura. RSV immunization Vilnius University Hospital Santaros Klinikos, Children ‘s Hospital in 2020 – 2025. Proportion of patients who received a full and incomplete (< 5 doses of palivizumab per season) course of RSV immunization.

5.2. NEW ERA FOR RSV IMMUNOPROPHYLAXIS IN GERMANY

RSV is a burden in health care worldwide and therefore the constant progress in developing more effective immunoprophylaxis tactics is crucial. Currently, late studies from Germany show an impressive progress in the concept of RSV prevention for high-risk infants as well as the older population. The current disease burden under the usage of palivizumab for high-risk infants shows approximately 12.5 million symptomatic patients with about 35,800 hospital admissions with 2600 children being treated at the intensive care unit (55). The mortality of RSV in Germany lies up to 213 deaths each year for all age groups (55). In contrast to Lithuania, in Germany the European commission introduced the licensed monoclonal antibody nirsevimab in September 2023 for preterm babies as well as children who are not prematurely born (56). The new product is about to replace the 5-dose injection scheme with palivizumab. There are benefits that argue in favor of the change of the substances as this study proved. According to this paper, replacing the current RSV prevention program with nirsevimab would help to lower RSV disease and make logistical

management simpler due to the single-dose schedule, in contrast to palivizumab which requires numerous doses during the season (55). Furthermore, the study describes the results of immunizing also non-high-risk infants between the age of 1-5 months. They demonstrate a positive result from including all infants and show a probable reduction of hospitalization of 18% annually (55). The question is whether preventive products should be available only to neonates and infants with specific risk factors or if, for a long-lasting improvement in health care facilities, all infants should have the option to be immunized. To achieve the maximum of protection it is crucial to stay consistent in the prophylaxis plan or to even make it mandatory as other vaccines. As children are not the ones who decide whether they will receive the injection it is even more important to discuss how parents influence the outcome of RSV prevention. A German paper describes the influence parents might have on the immunization program against respiratory syncytial virus. An online survey on demographics, socioeconomic status, mental health, RSV knowledge, attitudes regarding general childhood, and RSV immunoprophylaxis was filled out by parents of infants/children aged 0 to 36 months. The poll was carried out in the German region of Regensburg between February and June of 2023 (57). Further, the results of the questionnaire are summarized in the following. The box plot displays parental RSV worries for each of the three groups according to their openness regarding the administration of a monoclonal antibody (Figure 14). With a wide range of answers, parents who are willing to get their infant immunized have the highest concern regarding the procedure. With a somewhat smaller range, the group that is still undecided exhibits mild concerns. The lowest concerns arise among parents who refuse prophylaxis for their infant. In general, greater readiness to get their children protected with the injection against RSV is linked to higher levels of anxiety about RSV infection. There are several factors that influence the way of thinking and the decision making of the parents. For instance, lack of knowledge about either the virus itself, or the scheme of monoclonal antibody application offer offered by the health ministry in their country (57). Additionally, from the parental side of view the decisions are influenced by trust issues or through exchange with other parents about their experience with either the infection, the immunization process or both (57). Since the child's safety and health are the highest priority for parents it is not unexpected that such actions are questioned or carefully considered. Langer et. al. (2024) mentions that the willingness for immunizing the child is higher in families from

higher socioeconomic standards, as well as those who have already experienced several hospitalizations due to previous respiratory tract infections or have had a preterm baby who required more medical attention than usual (57). Overall, it is noted by the study that those parents who are willing to participate in RSV prevention strategies via monoclonal antibody usage, have more worries, and this is to be explained by their high knowledge about possible complications of RSV infection and therefor ironically, their willingness to agree on this measure is as high as their anxiety. The opposite group of parents, those who show no willingness might decide so due to lack of information about the disease, socioeconomic issues, no personal experience, and therefore no trust in new medical advises regarding RSV immunization, that are approaching the German market.

While parent's knowledge, experience, and confidence are contributing factors for the success of immunization programs, the introduction of nirsevimab in Germany represents a promising milestone in RSV immunoprophylaxis, showing greater opportunities to protect every child without categorizing them by risk status.

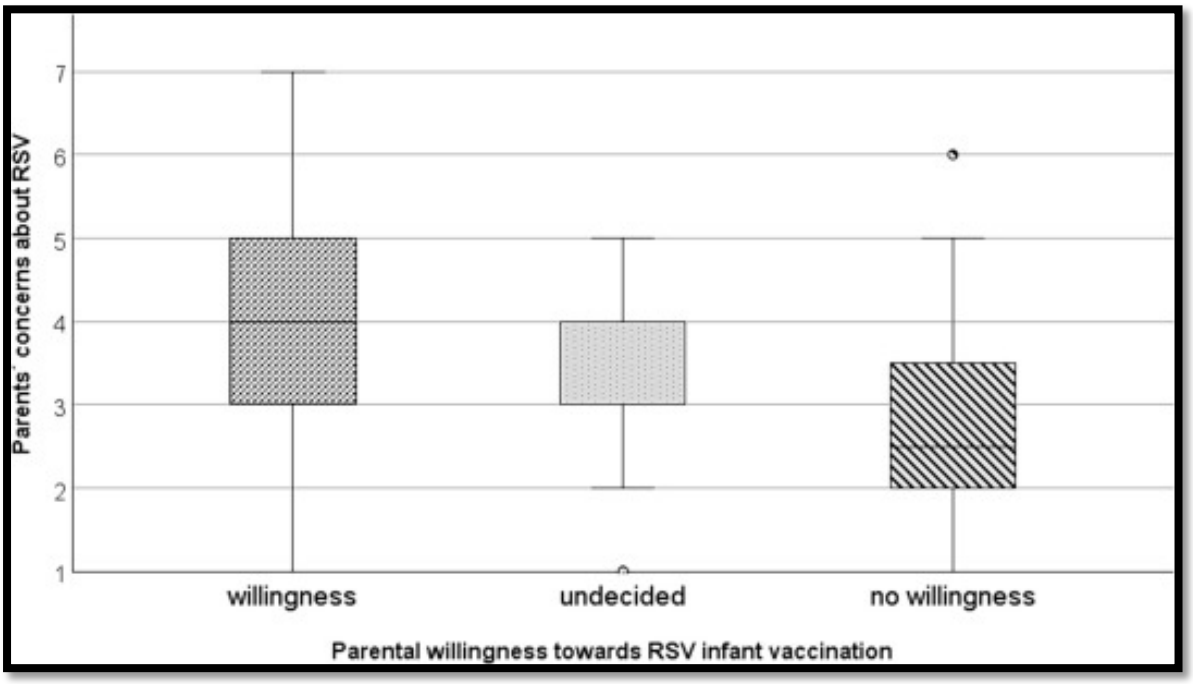

Figure 14. A scale from 1 (not at all concerned) to 7 (very concerned) was used to gauge parents' concerns about RSV disease, and the results were plotted against their will to immunize their kids (58)

6. CONCLUSIONS

1. Respiratory syncytial virus (RSV) remains a major cause of acute lower respiratory infections in neonates and infants due to their immature immune systems and limited maternal antibody protection, often resulting in hospitalization and long-term respiratory complications, especially for the pediatric patients that have comorbid medical conditions.

2. The COVID-19 pandemic significantly disrupted the typical RSV seasonal occurrence, resulting in almost no reported cases of RSV during the pandemic time. Following, infection peaks occurring unusually early in the post-pandemic years, influenced by changes in public health measures and altered population immunity.

3. Currently, Lithuania continues the 5-dose injection scheme with palivizumab for the immunoprophylaxis. At VUH SK the administration with palivizumab is limited for preterm infants and those who suffer from underlying conditions that account them as a high-risk population.

4. Recent guidelines favor the use of nirsevimab over palivizumab due to its longer-lasting protection as it offers a prolonged duration of action. Additionally, it requires only a single-dose administration, with recommendations of the usage of nirsevimab to all infants regardless of risk status; several European countries, such as Germany, have already adopted nirsevimab for infant immunization.

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