Chapter One

Introduction

1.1 Background to the Study

Respiratory Syncytial virus (RSV) is one of the most common and severe upper respiratory infectious disease in children (5 years and below) and older adults (above 65 years) worldwide[1]. RSV belongs to the family Paramyxoviridae and is the leading cause of lower respiratory tract infections in infants and older adults. RSV is an enveloped, non-segmented, negative strand RNA virus. It is the most complex of the Paramyxoviridae family in terms of gene and protein[2]. Studies have shown that older adults and children 5 years and below are more prone to respiratory viruses. Specifically, it is associated with 22% of all severe acute lower respiratory infection which has resulted in 66,000 to 119,000 deaths in children under 5 years in 2015. Due to its high contagiousness, the respiratory syncytial virus causes significant illness and mortality in society[4].

Respiratory syncytial virus (RSV) is one of the most serious pathogenic pediatric infections and is associated with a high rate of morbidity and mortality[5]. There is still no effective and secure vaccination on the market despite substantial research into Animal models, clinical indicators, diagnosis techniques, epidemiology, and the immunobiology of infection. The primary histopathologic hallmarks of RSV infection include acute bronchiolitis, mucosal and submucosal edema, and luminal obstruction by cellular ebris, which are sloughed epithelial cells mixed with macrophages, fibrin strands, and some mucus[6]. A and B are the two primary antigenic subgroups of the one RSV serotype. Co-circulating strains of both kinds occur often.but subtype A typically is the most prominent. RSV infections in temperate regions exhibit a distinct similarity to the human illness. Notably, children hospitalized throughout early childhood or infancy due to RSV have a significantly increased frequency of asthma[7].

But there hasn't been much research done on the likely genes that could account for this rise in vulnerability. Asthma tends to develop afterwards as a result of an atopic predisposition which is less important than the pathogenic inflammatory response, which uses chemokines, cytokines, and their corresponding preceptors[8]. Both the development of RSV vaccinations and the use of more modern antiviral medications to treat illness are undergoing extensive evaluation[9]. Determining the natural history of RSV and the potential effects of co-infection are also receiving a lot of interest. The connection between RSV bronchiolitis, other virally caused inflammatory reactions, and asthma must undoubtedly be further studied[10].

RSV has been identified to be associated with 22 percent of all severe acute lower respiratory infections and this has resulted in 66,000 to 199,000 deaths in children under the age of 5 years in 2015. In the United States, about 2.1 million younger than five years old visit outpatient clinic due to RSV[11]. In comparison with Influenza, RSV causes about 137 deaths per year in the US, while influenza causes about 38 deaths per year among kids under the age of four. RSV was also ranked third most important cause of pneumonia death in infants after *Haemophilus influenza* and *Streptococcus pneumonia* hence, RSV is increasingly recognized, not only in infants, but also in older adults[12].

The leading cause of paediatric pneumonia that require hospitalization in nations with low to moderate incomes throughout Africa as well as Asia has been attributed to RSV[13]. Its prevalence in Nigeria is about 34% as reported among children under the age of 5 years[14]. The diagnosis, put into consideration; the time of year and symptoms, laboratory and imaging test are then required for a confirmatory diagnosis. The laboratory investigations include blood tests which comprises leucocyte counts, virus and or bacteria identification. The imaging test usually required is Chest X-rays to check for inflammation of the lungs[15].

RSV like other respiratory tract infections share common symptoms. Influenza, Roseola infantum, Rotavirus infection, Rubella, Subacute Sclerosing Panencephalitis (SSPE) including Coronavirus all share majority of the following symptoms; congestion, runny nose, fever, cough and sore throat, fatigued, breathing difficulties, barking or wheezing cough, which in severe case result in pneumonia or bronchiolitis[16]. Early-life viral infection causes acute illness and can be connected to the emergence of wheezing and asthma when one ages. The at-risk population include infants of ages below 5 years and adults above 65 years, factors associated with this include; immature immunity in case of infants and low immunity due to old age in adults[17].

A contagious illness known as coronavirus disease 2019 (COVID-19) is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and spreads from person to person by respiratory droplets[18]. The infectious disease that is currently causing the 2019–2020 coronavirus pandemic[19], originated in Wuhan, the capital of Hubei Province, China, in December of 2019. From there, it traveled around the world. By April 6, 2020, the virus has spread to nearly every country in the world, resulting in over 1.6 million confirmed cases and 97,179 deaths, almost all of which occurred in Europe. This COVID-19 outbreak has expanded extremely swiftly[20].

Through the inhalation of aerosols from an infected person, COVID-19 is spread[21]. Potential risk factors for serious sickness and morality have primarily been found to be individuals with pre-existing conditions (such as hypertension, diabetes, lung disease, cancer, and cardiac disease), children, and old age[22]. For COVID-19, no antiviral vaccine or medication has been developed as of now. Its transmission, distribution, prevention, treatment, and pathogenesis are all subjects of additional research. The World Health Organization recommended preventing close contacts and medical personnel from contracting the disease in order to stop

person-to-person transmission[23]. The World Health Organization (WHO) on the 13th of October 2020, announced that routine handwashing, social segregation, hand sanitizer use, and respiratory hygiene (covering the mouth and nose when coughing or sneezing) are the primary protective measures to reduce the risk of the COVID-19 infection. Furthermore, to lower the danger of infection and illness spread, the general public must keep a distance of at least one meter. In addition, make putting on of nose mask a compulsory thing while in the company of people in a commonplace. Also, meet individuals outside rather than in 3Cs (places that are closed, crowded, or involve close contact[24].

All over the world, along with WHO, the majority of the government supported and imposed a severe lockdown at an early stage of COVID-19 since it was believed to be one of the best and most effective methods for controlling the current pandemic; it could possibly be more beneficial if carried out with integrity[25]. Authorities in various countries announced two weeks and then three weeks' lockdown, respectively, which was decided to extend due to the increased number of cases. The lockdown decision was not easy for the governments because it was supposed to affect the economy and the public badly. Along with major issues, the general public also faced sleep disturbance problems, anxiety, and depression due to lockdown.

Common symptoms of COVID-19 include inflammation of the upper respiratory tract and symptoms similar to the flu, such as sneezing, coughing, sinus obstruction, and mucous secretions from the nose[26]. After that, the temperature seems to rise to approximately 39 degrees or more during days 7-10, and then the person may feel a partial improvement until the end of the 2-wk period. While the majority of cases result in mild symptoms, some progress to acute injury to the lower respiratory tract and pneumonia. In addition to affecting

the respiratory system, there is a high risk of death in elderly people and people of all ages who suffer from serious health conditions, such as heart disease, lung disease, and diabetes[27].

All viruses in the *Nidovirales* order are enveloped, non-segmented positive-sense RNA viruses. They all contain very large genomes for RNA viruses, with some viruses having the largest identified RNA genomes, containing up to 33.5 kilobase (kb) genomes[28]. Other common features within the *Nidovirales*order include: a highly conserved genomic organization, with a large replicase gene preceding structural and accessory genes; expression of many non-structural genes by ribosomal frameshifting; several unique or unusual enzymatic activities encoded within the large replicase–transcriptase polyprotein; and expression of downstream genes by synthesis of 3 nested sub-genomic mRNAs[29]. In fact, the *Nidovirales* order name is derived from these nested 3′ mRNAs as *nido* is Latin for "nest." The major differences within the Nidovirus families are in the number, type, and sizes of the structural proteins. These differences cause significant alterations in the structure and morphology of the nucleocapsids and virions[30].

Coronaviruses are a family of enveloped, single-stranded, positive-strand RNA viruses classified within the Nidovirales order. This coronavirus family consists of pathogens of many animal species and of humans, including the recently isolated severe acute respiratory syndrome coronavirus (SARS-CoV)[31]. In the event of COVID-19, it has become important to accurately diagnose upper respiratory viruses since they share similar symptoms. Consequently, this study will be designed to detect and characterize RSV among older adults and children 5 years and below that tested negative for COVID-19. RSV has never really been identified as a major cause of infection among kids and older adult hence the need for the study[32]. Many studies have been carried out on RSV but doing it again will sensitize the community and health facilities to look out for RSV as a major cause of respiratory infection

in children and older adults and also bring it to their knowledge that RSV can be a co virus in other infections[33].

1.2 Statement of the Problem

Ribavirin released in aerosol form for the treatment of RSV demonstrate faster clearance, decreased viral shedding and shorter stay in hospital. Palivizumab is a humanized monoclonal antibody specifically targeted at RSV infection and it is licensed for RSV prophylaxis in premature infants and those infants given birth to with cardiopulmonary disorders[34].

Also, in the older adult with suppressed immunity. The drugs mentioned are some treatment options for RSV which is not available for the novel COVID-19, although certain drugs and vaccines are on clinical trial phase, a wrong diagnosis based on just the symptoms which is almost the same in most respiratory viruses may result in extended use of drugs and unnecessary treatment plans which include isolation and other intensive care with high-cost implication, post isolation center psychological effect and even health implication[35].

The identification of the specific organism causing an infection is necessary, especially when such causatives possess similar symptoms with other infections. This is necessary to specifically treat an infectious disease and will make treatment easier and specific, hence problems such as drug resistance may be reduced. Therefore, the aim of this study is to identify a contributing factor of viral respiratory illnesses that present similar symptoms and their prevalence in Ibadan, southwest Nigeria.

1.3 Justification of the Study

RSV is a respiratory illness that is common in young children and older adult and can be a co infection in respiratory illnesses, also other respiratory viruses can also co infect children, and older adult hence the need for the study.

Without proper diagnosis, infection with RSV can be fatal, mortality and morbidity will increase. Rapid detection of RSV and co-infected virus is required to inform best practices and treatment to avert mortality rate of children and older adult

This study will add to the body of Knowledge by sensitizing the health workers, the community and the policy makers to be aware of the virus RSV which can also coinfect with Sars-Cov- 2 Influenza A and B.

1.4 Aims and Objectives of the Study

The aim of this study is to determine the prevalence of RSV among Covid-19 older adult and children 5 years and below in Ibadan, Southwest Nigeria

The general objective of this study is to detect and characterize RSV among older adults and children 5 years and below that tested negative for COVID-19.

Specific Objectives are to:

i. Determine the prevalence of RSV among children 5 years and below and older adults that has been tested negative for COVID-19.
ii. Determine the prevalence of other respiratory viruses (flu A, Flu B) among children and other adult that tested negative for COVID-19 and the association of coinfection of RSV with other upper respiratory viruses.
iii. Identify genetic variance of RSV from participants in the senatorial Districts of Ibadan, Southwest.

1.5 Research Questions

1. What is the prevalence of RSV among COVID-19 negative children 5 years and below in the senatorial district of Ibadan, Oyo State Nigeria?
2. What is the prevalence of RSV among COVID -19 negative Older Adults in the senatorial district of Ibadan, Southwest Oyo State Nigeria?
3. What is the prevalence of other respiratory viruses (Flu A and Flu B) among COVID-19 negative children in the senatorial district of Oyo State Nigeria?
4. What is the prevalence of other respiratory viruses among COVID-19 negative older adults in the senatorial district of Oyo State Nigeria?
5. What is the association of co-infection among COVID-19 negative children in the senatorial District of Ibadan Southwest Nigeria?
6. What is the association of coinfection among COVID-19 negative older adults in the senatorial district of Ibadan Southwest Nigeria?

1.6 Hypothesis

Ho1: Respiratory Syncytial virus (RSV), Influenza A and B can be found in samples tested negative for COVID-19 in older adults and children 5 years and below.

1.7 Significance of the Study

It is important to note that children or adult suspected for COVID-19 can also be suffering from other ailment like RSV and other co infections like influenza A and B and thus other co infections should also be looked out for when checking for COVID-19. This study will show that a sample that is negative for COVID -19 can have other co infection viruses embedded in the samples

1.8 Scope of the Study

The study covers children that are 5 years and below that have been tested negative for COVID-19 and also older adults that have been tested negative for COVID -19. It makes use of adults and children's samples that have been stored (Archived) in -80^{0}C ultralow freezers collected from senatorial District of Ibadan Southwest Nigeria

1.9 Limitation of the Study

I could not relate directly with the owners of the samples used because the data used were secondary data (Archived Samples). Some of the adult participant did not disclose their age for security reasons.

1.10 Operational Definitions of Terms

Immunobiology; This is the study of the immune system that confers protectionagainst infectious diseases. This complex system is also involved in the rejection of grafted tissues in allergy and in autoimmunity

Pediatrics: This is the branch of science that deals with children and their diseases,

Undisclosed; This means that participants did not disclose their particulars e.g., age, sex or local government area for security reasons.

COVID-19: This is an infectious disease caused the SARS-COV-2 virus. It is the official name given by the World Health Organization (WHO to the disease. The new corona virus first surfaced in Wuhan, China in 2019 and spread around the globe

Endnotes

1. C. Papan, M.W. Willersinn, C.W. Weiß, M.K. Karremann, H.S. Schroten & T.T Tenenbaum, *Antibiotic Utilization in Hospitalized Children under 2 years of age with Influenza or Respiratory Syncytial Virus Infection–a Comparative, Retrospective Analysis*, **BMC Infectious Diseases**, 20(1), 2020, 1-10.

2. C.A. Azzari, E.B. Baraldi, P.B.Bonanni, E.B. Bozzola, A.C. Coscia, M.L. Lanari & F.M. Mosca, *Epidemiology and prevention of respiratory syncytial virus infections in children in Italy***, Italian Jounal of Pediatrics**, 47, 2021**,** 1-12.

3. J. A. Coultas, R. Smyth, & P. J. Openshaw, *Respiratory Syncytial Virus (RSV*): *A Scourge from Infancy to Old Age*, **Thorax**, 74(10), 2019, 986-993.

4. S. Zhang, L. Z. Akmar, F. Bailey, B. A. Rath, M. Alchikh, B. Schweiger, & H. Nair *Cost of Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection Management in Young Children at The Regional and Global Level: A Systematic Review and Meta-Analysis*, **The Journal of Infectious Diseases,** 222, 2020**,** 680-687.

5. Z. Haddadin, S. Beveridge, K. Fernandez, D. A. Rankin, V. Probst, A. J. Spieker, & N. Halasa, *Respiratory Syncytial Virus Disease Severity in Young Children*, **Clinical Infectious Diseases** *73*(11), 2021, 4384-4391.

6. X. Li, L. Willem, M. Antillon, J. Bilcke, M. Jit, & P. Beutels, *Health and Economic Burden of Respiratory Syncytial Virus (RSV) Disease and The Cost-Effectiveness of Potential Interventions Against RSV Among Children Under 5 Years in 72 Gavi-Eligible Countries*, **BMC Medicine,** 18, 2020, 1-16.

7. O. Manuel, M. Estabrook, *American Society of Transplantation Infectious Diseases Community* of *Practice RNA Respiratory Viral Infections in Solid Organ Transplant recipients: Guidelines from The American Society of Transplantation Infectious Diseases Community of Practice*, **Clinical Transplantation**, 33(9), 2019, 13511.

8. J. Kubale, G. Kuan, L. Gresh, S. Ojeda, E. Azziz-Baumgartner, N. Sanchez, & A. Gordon, *Assessing the Incidence of Symptomatic Respiratory Syncytial Virus Illness within a Prospective Birth Cohort in Managua, Nicaragua*, **Clinical Infectious Diseases,** 70(10), 2020, 2029-2035.

9. M. Bardsley, R. A. Morbey, H. E. Hughes, C. R. Beck, C. H. Watson, H. Zhao, & A. J. Elliot, *Epidemiology of Respiratory Syncytial Virus in Children Younger than 5 Years in England During The COVID-19 Pandemic, Measured By Laboratory, Clinical, and Syndromic Surveillance: A Retrospective Observational Study*, **The Lancet Infectious Diseases,** 23(1), 2023, 56-66.

10. V. Salimi, M. Viegas, A. Trento, C. N. Agoti, L. J. Anderson, V. Avadhanula, & U. J. Buchholz, *Proposal for Human Respiratory Syncytial Virus Nomenclature below The Species Level*, **Emerging Infectious Diseases,** 27(6), 2021, 1-3.

11. J. Fourgeaud, J. Toubiana, H. Chappuy, C. Delacourt, F. Moulin, P. Parize & P. Frange, *Impact of Public Health Measures on the Post-COVID-19 Respiratory Syncytial Virus Epidemics in France*, **European Journal of Clinical Microbiology & Infectious Diseases,** 40, 2021, 2389-2395.

12. F. Scaggs Huang, D. I. Bernstein, K. S. Slobod, A. Portner, T. Takimoto, C. J. Russell, & J. L. Hurwitz, *Safety and Immunogenicity of An Intranasal Sendai Virus-Based Vaccine for Human Parainfluenza Virus Type I and Respiratory Syncytial Virus (SeVRSV) in Adults*, **Human Vaccines & Immunotherapeutics,** 17(2), 2021, 554-559.

13. F. M. Marty, R. F. Chemaly, K. M. Mullane, D. G. Lee, H. H. Hirsch, C. B. Small & S. S. Dadwal, *A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multicenter Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of Presatovir in Hematopoietic Cell Transplant Recipients with Respiratory Syncytial Virus Infection of the Lower Respiratory Tract*, **Clinical Infectious Diseases,** 71(11), 2020, 2787-2795.

15. F. Scaggs Huang, D. I. Bernstein, K. S. Slobod, A. Portner, T. Takimoto, C. J. Russell, & J. L. Hurwitz, *Safety and Immunogenicity of An Intranasal Sendai Virus-Based Vaccine for Human Parainfluenza Virus Type I and Respiratory Syncytial Virus (SeVRSV) in Adults,* **Human Vaccines & Immunotherapeutics,** 17(2), 2021, 554-559.

16. Z. Haddadin, S. Beveridge, K. Fernandez, D. A. Rankin, V. Probst, A. J. Spieker, & N. Halasa, *Respiratory Syncytial Virus Disease Severity in Young Children*, **Clinical Infectious Diseases,** 73(11), 2021, 4384-4391.

17. J. J. G. T. Van Summeren, C. Rizzo, M. Hooiveld, J. C. Korevaar, J. M. T. Hendriksen, M. L. A. Dückers, & J. Paget, *Evaluation of a Standardized Protocol to measure the Disease Burden of Respiratory Syncytial Virus Infection in Young Children in Primary Care*, **BMC Infectious Diseases,** 21(1), 2021, 1-10.

18. M. P. Griffin, Y. Yuan, T. Takas, J. B. Domachowske, S. A. Madhi, P. Manzoni, & J. P. DeVincenzo, *Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants*, **New England Journal of Medicine,** 383(5), 2020, 415-425.

19. *World Health Organization. Coronavirus* (COVID19). https://who.sprinklr.com/. Accessed April 6, 2020.

20. D. S. Hui, E. I. Azhar, T. A. Madani, F. Ntoumi, R. Kock, O. Dar & E. Petersen, *The Continuing 2019-nCoV Epidemic Threat of Novel Coronaviruses to Global Health-The latest 2019 Novel Coronavirus Outbreak in Wuhan, China*, **International Journal of Infectious Diseases,** 91, 2020, 264-266.

21. *World Health Organization. Coronavirus Disease (COVID-19) Advice for the Public, 2020.*

22. Y. Bai, L. Yao, T. Wei, F. Tian, D. Y. Jin, L. Chen & M. Wang, *Presumed Asymptomatic Carrier Transmission of COVID-19*, **Jama,** 323(14), 2020, 1406-1407.

23. S. Tian, N. Hu, J. Lou, K. Chen, X. Kang, Z. Xiang, & J. Zhang, *Characteristics of COVID-19 Infection in Beijing*, **Journal of Infection,** 80(4), 2020, 401-406.

24. *World Health Organization. Coronavirus Disease (COVID-19) Advice for The Public*, 2020.

25. *World Health Organization. Coronavirus Disease (COVID-19) Advice for The Public*, 2020

26. M.R. Gualano, G. Lo Moro, G. Voglino, F. Bert & R. Siliquini, *Effects of Covid-19 Lockdown on Mental Health and Sleep Disturbances in Italy*, **International Journal of Environmental Research and Public Health,** 17(13), 2020, 4779.

27. L.E. Kushner, A.R. Schroeder, J. Kim, & R. Mathew, *"For COVID" or "With COVID": Classification of SARS-CoV-2 Hospitalizations in Children*, **Hospital Pediatrics,** 11(8), 2021, 151-156.

28. C. Hopkins, *Loss of Sense of Smell As Marker of COVID-19 Infection. Ear, Nose and Throat Surgery Body of United Kingdom, Retrieved March 28, 2020*.

29. M.A. Rohaim, R.F. El Naggar, E. Clayton, & M. Munir, *Structural and Functional Insights into Non-Structural Proteins of Coronaviruses*, **Microbial Pathogenesis,** 150 2021, 104641.

30. R. Vijayan & S. Gourinath, *Structure-based Inhibitor Screening of Natural Products against NSP15 of SARS-CoV-2 revealed Thymopentin and Oleuropein as Potent Inhibitors*, **Journal of Proteins and Proteomics**, 12, 2021, 71-80.

31. A. Modrego, D. Carlero, R. Arranz, & J. Martín-Benito, *CryoEM of Viral Ribonucleoproteins and Nucleocapsids of Single-Stranded RNA Viruses*, **Viruses,** 15(3), 2023, 653.

32. K. E. Hanson, M. M. Azar, R. Banerjee, A. Chou R. C. Colgrove, C. C. Ginocchio, & A. M. *Caliendo, Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations from the IDSA's Diagnostics Committee*, **Clinical Infectious Diseases,** 71(10), 2020, 2744-2751.

33. E. Grellet, A. Goulet & I. Imbert, *Replication of the Coronavirus Genome: A Paradox among Positive-Strand RNA Viruses*, **Journal of Biological Chemistry,** 2022, 101923.

34. N. Gupta & S. Ahmed. Coronavirus: *An Overview of Genetics and Transmission Stages*, **Health Informatics and Technological Solutions for Coronavirus (COVID-19),** 2021, 41-63.

35. J. P. Sosa, M.M. F. Caceres, J. R. Comptis, J. Quiros, F. S. *Príncipe-Meneses, A. Riva-Moscoso & S. Marian, Effects of Interferon Beta in COVID-19 Adult Patients: Systematic Review*, **Infection & Chemotherapy,** 53(2), 2021, 247.

36. H. H. Nam, & M. G. Ison, Respiratory Syncytial Virus, In **Seminars in Respiratory and Critical Care Medicine** 42(6), 2021, 788-799.

Chapter Two

Literature Review

2.1 History of Respiratory Syncitial Virus

Respiratory Syncytial Virus (RSV) is a common virus that can be found all over the world. The leading cause of infant morbidity from respiratory infections[1]. By the age of two years nearly all children have been infected and can cause severe bronchiolitis and pneumonia in this age group. In the USA, the virus infects about 100% of children by the time they are 2 to 3 years old. Several hundred newborns may pass away from the illness directly, and an additional several thousand deaths may be linked to RSV-related complications[2]. According to estimates from the World Health Organization, (RSV) causes 160,000 fatalities and 64 million illnesses worldwide per annum[3].

Human respiratory syncytial virus (hRSV) is a Human Orthopneumovirus that causes syncytial histopathology in the respiratory tract of infected and diseased children. It is a major cause of lower respiratory tract infection and increases treatment attention, cost of treatment from debilitation to resuscitation and convalescence during infancy and childhood[4]. It is very contagious. Palivizumab, a preventive drug, can be used to prevent RSV in preterm newborns (those born at less than 35 weeks of gestation), children with specific congenital heart abnormalities (CHD) or bronchopulmonary dysplasia (BPD), and infants with congenital airway malformations. Only supportive care, such as oxygen therapy, more sophisticated breathing assistance, or nasal high flow oxygen, is used as a kind of treatment[5]. RSV is spread through contaminated air droplets and can cause outbreak both in the community and in the hospital settings[6]. Following the initial contamination through the eyes or nose, the virus will infect the epithelial cells of the upper and the lower airway, causing inflammation, cell damage and airway obstruction. While it primarily affects newborns, it is

being known that it is a major source of sickness in older individuals and can frequently be fatal for those with compromised immune systems. The incubation period of RSV respiratory disease is estimated to be three to five days. In people with compromised immune systems, viral shedding is greatly extended and can last for many months[7].The clinical manifestations range from mild upper tract illness, infection in middle ear which progresses into acute otitis media, croup, to apnoea in premature infants, pneumonia and bronchiolitis. The virus replicates in the nasopharynx during the early stages of the illness[8]. A productive cough and mild to moderate nasal congestion with evident rhinorrhea are typical signs of an upper respiratory tract infection[9]. Early on in the illness, a mild fever may appear, and before full recovery, symptoms may last one to three weeks. Tachycardia (rapid breathing of more than 60 to 70 breaths per minute), wheezing, and/or rales are signs of lower respiratory tract disease and typically start up to three days after the commencement of rhinorrhea. In the early stages of the sickness, the virus multiplies in the nasopharynx[8]. A productive cough, moderate nasal congestion, and obvious rhinorrheaare. Typical signs of an upper respiratory tract infection[9]. Early on in the illness, mild fever may appear, and before full recovery, symptoms may last one to three weeks. Tachycardia (rapid breathing of more than 60-70 breaths per minute), wheezing, and/or rales are signs of lower respiratory tract disease and typically show up to three days after the onset of rhinorrhea[10]. These signs show that the virus has entered the bronchi and bronchioles. A chest radiograph shows flattened diaphragms and hyperinflation.[10]. These signs show that the virus has entered the bronchi and bronchioles. A chest radiograph shows flattened diaphragms and hyperinflation. Middle and higher lobes may get impacted by an interstitial pneumonia if the RSV extends to the alveoli further[11]. Such individuals have significant respiratory distress, including deep retractions and grunting respirations, along with tachypnea. Hypoxemia, acidosis, and dehydration all dramatically raise the risk of cardiovascular failure. Complete bronchiolar blockage is particularly

common in people with compromised immune systems and small infants with very short bronchioles[12]. Additionally, there is a higher chance of vomiting, which is frequently a sign of respiratory distress and can make gastroesophageal reflux more likely. With dehydration as well as decreased in oral intake. Risk factors for morbidity and mortality during RSV infection include premature infants born at 30-35 weeks' gestation, HIV-positive people, children with cyanotic congenital heart disease, and other immunosuppressive treatments such as bone marrow transplant[13].

The single-stranded, negative-sense RNA virus known as the human respiratory syncytial virus is a member of the Pneumoviridae family[14]. Two major antigens, referred to as the A and B subtypes, are commonly used to classify RSV. One of the most prevalent respiratory viruses is the respiratory syncytial virus (RSV). The elderly and patients with immune system deficiencies are also affected, in addition to young children[15]. The risk of developing a severe RSV infection increases with age, specific comorbidities such as severe lung illness, transplant recipients, and those with compromised immune systems. RSV is more common in winter in countries with moderate climates. In contrast, RSV outbreaks can be seen in tropical and subtropical nations during cooler or rainier months[16]. Due to a shortage of RSV vaccination, human respiratory syncytial virus infection has become a significant public health concern that has resulted in high hospitalization and fatality rates[17]. Clinicians and researchers have recognized parallels and differences between RSV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the corona virus disease 2019 (COVID-19) era. Public health and social measures (PHSMs), which include personal protective measures including mask use, hand cleanliness, and social distancing, measures to protect the environment, and monitoring and interventive measures, have been widely implemented throughout the COVID-19 era. PHSMs are crucial in the fight against SARS-CoV-2 spread[18]. Other respiratory viral illnesses have also been greatly impacted by the

introduced PHSMs. During the COVID-19 era, numerous studies have demonstrated a striking decline in the frequency of RSV and other common respiratory pathogens[19]. The underlying nature of the link might be more complex, despite the fact that it seems to be a straightforward direct correlation[20].

Two respiratory infections that share certain symptoms are respiratory syncytial virus (RSV) and coronavirus[21]. The new coronavirus seems to pose a greater risk to individuals, particularly those who are older. Young children are at higher risk for human respiratory syncytial virus infection, but older adults and individuals with pre-existing medical conditions are also at risk. Viruses that commonly infect the respiratory tract are referred to as coronaviruses. The virus that causes COVID-19 is the most recent[22].

Despite the fact that, COVID-19 can affect children, the majority of cases that have been diagnosed so far are in adults. Additionally, adults are more prone to experience severe coronavirus symptoms, particularly if they are over 65 or suffer from a condition like diabetes, lung illness, or heart disease. RSV can also affect people of ages, but it's especially common in infants and young children[23]. Almost every children will be infected by the age of two. Most incidents are minor. However, specific children are more susceptible to developing a serious illness, such as:

Babies who are 6 months or younger; premature infants; children under 2 who have chronic lung or heart problems; kids with impaired immune systems; kids who are having difficulty in swallowing

More than 57,000 kids are hospitalized due to the human respiratory syncytial virus each year.

Adults and older children who contract RSV typically only experience mild symptoms resembling a cold. However, RSV can be severe for some people, particularly:

Those over 65, those with compromised immune systems and those suffering from heart or lung conditions[24].Respiratory Syncytial Virus (RSV) and COVID-19, are all highly contagious respiratory infections caused by viruses: The flu by influenza virus, COVID-19 by SARS-CoV-2 virus, and RSV by Respiratory Syncytial Virus. It is possible for a person to be infected with multiple viruses at the same time[25]. The flu is caused by the influenza virus and spreads easily during the winter months when people spend time together indoors. There are many strains of influenza virus, and the virus can change from year to year, which is why you should get a flu vaccine each year[26]. RSV is caused by the respiratory syncytial virus, a highly contagious virus that can infect children and adults. In adults and older children, RSV is typically a mild illness very similar to the common cold[27]. In infants and the elderly, the symptoms can be more severe while COVID-19 is caused by SARS-CoV-2, a new coronavirus. Coronaviruses are a family of viruses named for their corona-like shape. Sometimes, the general term "coronavirus" is used with COVID-19, but this is technically incorrect because there are many types of coronaviruses in this family, including SARS-CoV-1 which emerged in 2002 and other coronaviruses[28].

In the US, RSV causes 60,000–120,000 older persons to be hospitalized each year, and 6,000-10,000 of them pass away. The same viral droplets that are released into the air when an infected person coughs or sneezes serve as the primary means of transmission for both diseases. If the virus is on a surface and you touch it before putting your fingers in your mouth, nose, or eyes, you could become ill[29].

2.2 Virology of Human Respiratory Syncytial Virus (RSV)

Human Respiratory Syncytial Virus belongs of the subfamily Pneumovirinae in the family Paramyxoviridae, and the order Mononegavirales. Mumps, measles, and parainfluenza (types 1, 2, and 3) are a few additional RNA viruses that share similarities with human respiratory

syncytial virus. The Respiratory syncytial virus is an enveloped virus that possess a lipoprotein coat with a linear negative-sense RNA genome that measures between 120 and 200 nm. The RSV genome is around 15,000 nucleotides long and is made up of 10 mRNAs, each of which codes for a different viral protein. The structural proteins are divided into three functional categories: viral polymerase (L), phosphoprotein (P), and nucleocapsid protein (N). The RSV replicase is a protein complex that function as these proteins. [30] The fusion (F) and attachment (G) glycoprotein projections that are spiked on the outside of the outer envelope and lined internally with matrix protein (M) are what allow the RSV infection to start and spread because they adhere to the host cells. Another protein found in the viral envelope is (M2). A phosphoprotein, a polymerase protein (C), and a nucleoprotein make up the viral capsid. The G protein is of special importance since it varies more between and among the main antigenic groups of RSV than the other proteins do[31].

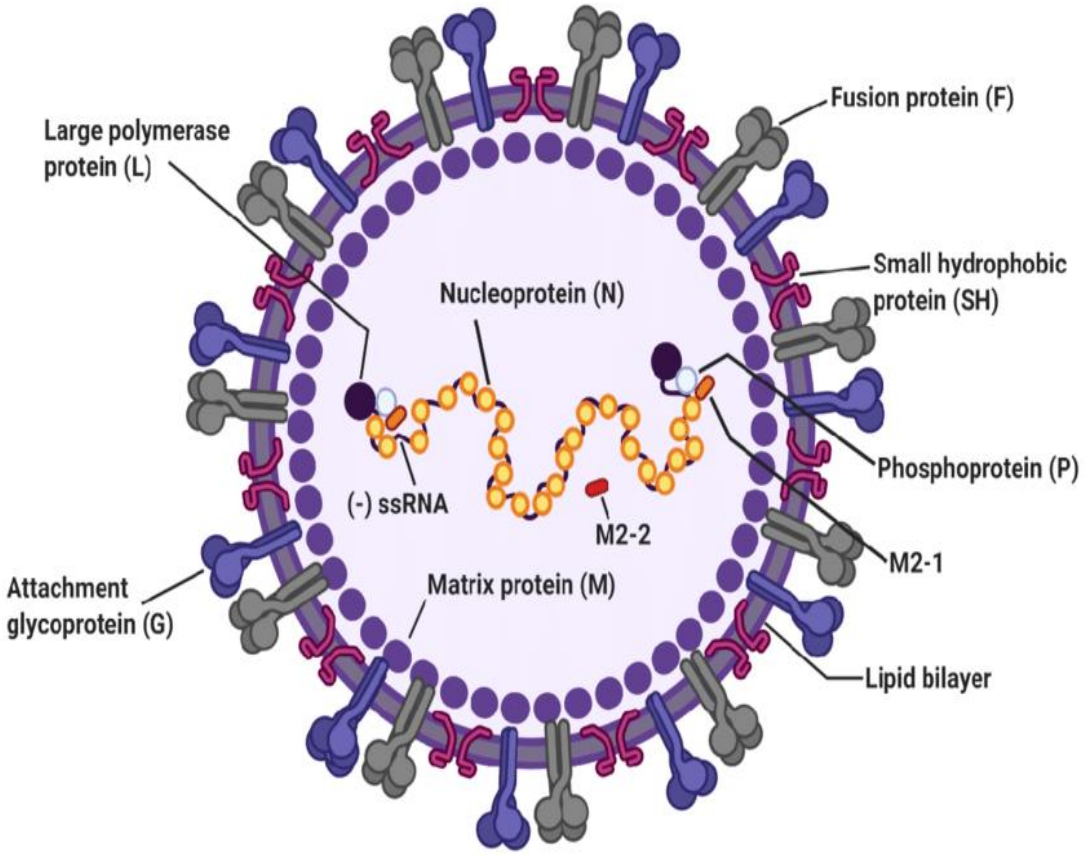


Figure 2.1: Structure of Respiratory Syncytial Virus

Source [30]

2.3 Replication of Human Respiratory Syncytial Virus (RSV)

RSV replication is limited to the respiratory mucosa and is not typically found outside of the bronchopulmonary tree[32]. The G protein starts the virus' attachment to the epithelial cell. After the F protein is broken down by the infected cell's proteolytic enzymes, the virus fuses with the epithelial cell membrane and enters the cytoplasm. The precursor has no fusion activity if it is not cleaved, which prevents virion penetration and prevents the viral particle from starting infection[33]. The viral nucleocapsid is released into the cell when fusion by F1 takes place in the extracellular environment's neutral pH. As a result, the virus can avoid internalization via endosomes[34]. The virus develops following replication by budding from the cell surface. In the cytoplasm, the progeny nucleocapsids develop before moving to the cell surface. The M protein, which serves to connect the viral envelope to the nucleocapsid, is crucial for particle formation[35]. The majority of host proteins are removed from the membrane during budding. Plasma membrane precursor proteins will be cleaved into active forms if the proper host cell proteases are present. Large syncytia will then be formed as a result of the neighboring cell membranes fusing as a result of the activated fusion protein[36].

Even in the absence of fully formed viral particles, the viral RNA can spread. The upper respiratory tract's epithelial cells are destroyed as a result of the infection[37]. RSV exposure causes humoral immune responses. IgM, IgG, and IgA are the only antibodies generated in response to primary RSV infection. An upper respiratory disease occurs because this reaction is weak and insufficient to eradicate the virus fully or stop it from replicating in the upper respiratory tract[38].

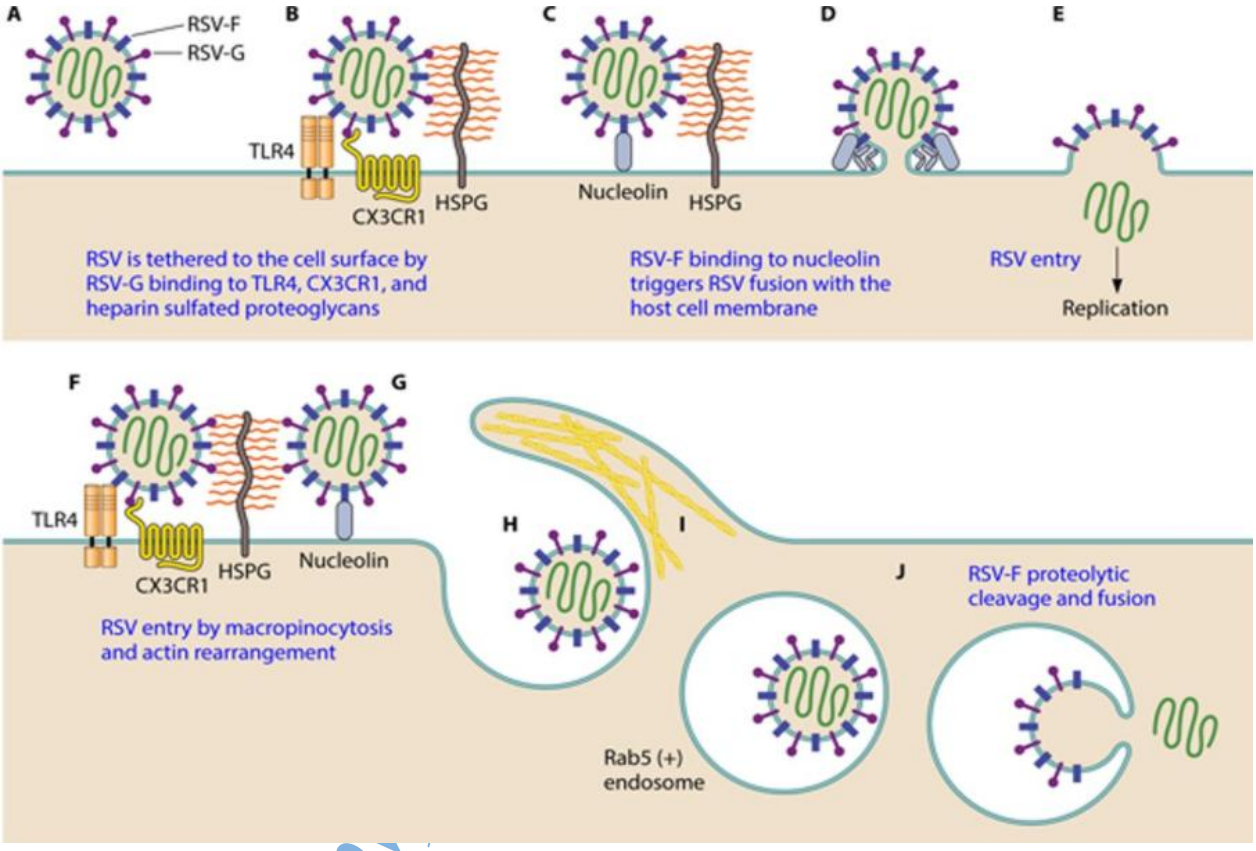


Figure 2.2: Respiratory Syncytial Virus Replication.

Source [32]

Although, Nasal epithelial cells are mostly infected by the Respiratory Syncytial virus. However, in some T and B cell immunodeficiency conditions, extra pulmonary disease progression has been noted. Significant emphasis has been paid to the link between RSV and asthma and reversible reactive airway disease in young children[39]. After original infection or reinfection with RSV, a considerable proportion of kids with a strong family history of allergy have shown recurrent wheeze for up to 5 to 7 years of age and developed airway illness[40]. The immune response to the first infection is relatively minimal, but with reinfection, the serum and respiratory mucosa exhibit a strong booster effect with prolonged immunologic reactivity. Immune responses specific to Th1 and Th2 cells, CD4 and CD8 receptors, and human infection have all been documented[41]. In addition, both natural and artificial (in vitro) infections cause the respiratory tract to produce proinflammatory and immunoregulatory cytokines and chemokines. The RSV virus will migrate throughout the lower respiratory tract in susceptible patients. The infection swiftly advances to the LRT in preterm newborns and immunosuppressed hosts[42]. Immunopathological reactions worsen lung damage when T cells kill the virus inside the lung. Tumor necrosis factor-alpha (TNF-alpha) and other proinflammatory cytokines and chemokines are released by infected cells, along with interleukins (IL-1, IL-6, and IL-8). These processes cause the airway lining and surrounding tissues to become inflamed by the activation of inflammatory cells such as macrophages, eosinophils, neutrophils, and T lymphocytes[43].

2.4 Classification of Respiratory Syncytial Virus

HRSV is a negative-sense, single-stranded RNA virus of the family Pneumoviridae Realm Riboviria Kingdom Ortonavirae phylum Negamavicota, Phylum Negamavicota, Class Monjiviricetes, Order Mononegavirales while genus Orthopneumovirus and Specie Human orthopneumovirus[44]. Its name is derived from the large cells known as Scynthia that form

when infected cells fuse 2x and 3x. RSV is the single most common cause of respiratory hospitalization in infants, and reinfection may occur in later life. It is an important pathogen in all age groups[45].

Based on their reactivity to monoclonal antibodies, respiratory syncytial virus strains were initially divided into two groups (A and B). The ability to characterize and categorize viruses in greater depth was subsequently made possible by the sequencing of viral genes[46]. Consequently, both the RSV-A and RSV-B groups contain a variety of genotypes. RSV genotypes are not, however, defined by a well-established system or a consensus. Relevantly, RSV has demonstrated a dynamic evolutionary process with discernible changes over time, including the emergence of new genotypes and the apparent demise of others. The appearance of RSV-A strains with a partial duplication of the G protein gene is the most remarkable development seen in recent years[47]. The mechanisms causing the formation of these viruses, as well as the epidemiological and clinical consequences of the observed modifications, have not yet been fully described, despite the fact that RSV-B strains with a comparable duplication have been in circulation for more than 20 years[48,49].

The genomic region of the G gene, which exhibits greater variation among viral strains, is typically utilized to differentiate and categorize RSV. According to a theory, immunological selection caused by antibodies against viral surface proteins such the G protein leads to the development of RSV variety. Recent research, however, indicates that such immunological systems might not be the cause of RSV variability[50]. RSV variability has implications for the design of diagnostic assays, antiviral treatments, and preventative methods (passive immunization and vaccines) and is a major feature that permits reinfections to happen throughout life. A good comprehension of the genetic diversity of the available viral sequences and their accurate genotype assignment should be helpful in order to investigate

this. The lack of agreement on current genotypes emphasizes the necessity for a thorough investigation. New viral genotypes have been identified by a number of publications, but the criteria employed to characterize them are inconsistent and unclear[51,52]. Additionally, because the G gene exhibits the greatest variety and enables strain classification, other viral genes have not received as much attention. Other genes, however, exhibit significant variation as well, and adjustments to them may potentially aid in genotype classification. In addition, mutations in genes other than the G gene might influence the virulence of the strain and the patterns of epidemiological circulation over time[53].

RSV sequences, including those of the G gene and the entire viral genome, have significantly increased in recent years and are now more readily available in GenBank. This makes it possible to conduct more thorough analyses, thereby enhancing the accuracy of genotype classification[54].

In their research, they examined every RSV-A sequence that is now accessible and contains the entire G gene ectodomain in order to define the traits of genotypes that have already been published. The NS1, NS2, N, P, M, SH, F, and L gene sequences were also examined, and genetic markers connected to particular genotypes were discovered. These findings contribute to the development of a framework for the classification of RSVs and aid in the comprehension of thr processes that give rise to the diversity of the virus[55].

2.5 Coronavirus (COVID- 19)

Coronavirus is known to cause the coronal virus infection which was later corona virus disease. It is a respiratory virus which belongs to the subfamily Orthocoronavirinae. The coronavirus disease 19 (COVID-19) is highly contagious and pathogenic viral infection that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)[56]. The coronaviridae family is made of a group of enveloped, large, single, and positive-stranded

RNA viruses and is known to cause common cold and diarrhea diseases in humans. Because of its phylogenic relation to the severe acute respiratory syndrome-like (SARS-like) viruses in bat, the possible primary reservoir could be bats[57].The virus as an RNA virus binds the host cells via its envelope lipid bilayer and releases its RNA into the cytoplasm resulting in a translation of the viral mRNA into viral proteins which assembles into new viruses and burst out of the cell. The viral receptor ACE2 is abundant in cells of several organ of the body including lung, heart, kidney and adipose tissue is the reason for the accompanied symptoms shown by the hosts[58].

In their research, they examined every RSV-A sequence that is now accessible and contains the entire G gene ectodomain in order to define the traits of genotypes that have already been published. The NS1, NS2, N, P, M, SH, F, and L gene sequences were also examined, and genetic markers connected to particular genotypes were discovered. These findings contribute to the development of a framework for the classification of RSVs and aid in the comprehension of the processes that give rise to the diversity of this virus. Respiratory syndrome coronavirus 2 (SARS-CoV-2)

Coronavirus disease 2019 (COVID-19) is a communicable disease transmitted by means of respiratory droplet from 1 person to another caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[59]. This infectious disease first appeared in Wuhan, the capital of China's Hubei Province in December of 2019 then spread globally, resulting in the ongoing 2019-2020 coronavirus pandemic[59]. The current COVID-19 epidemic has spread very quickly, and by April 6, 2020, the virus had reached almost all countries of the world, resulting in over 1.6 million confirmed cases and 97,179 deaths, with nearly all infections and deaths occurring in Europe[60].

Through the inhalation of aerosols from an infected individual, COVID-19 is spread. Potential risk factors for serious sickness and morality have primarily been found to be individuals with pre-existing conditions (such as hypertension, diabetes, lung disease, cancer, and cardiac disease), children, and old age[61]. For COVID-19, no antiviral vaccine or medication has been suggested as of yet. Its transmission, distribution, prevention, treatment, and pathogenesis are all subjects of additional research. The World Health Organization suggested keeping close contacts and medical personnel from contracting the disease in order to stop person-to-person transmission[62]. On October 13, 2020, the WHO announced that social seclusion, routine handwashing, the use of hand sanitizer, and respiratory hygiene (covering the mouth and nose when coughing or sneezing) are the main preventative strategies to lower the risk of COVID-19 infection and its dissemination. Furthermore, to lower the danger of infection and illness spread, the general public must keep a distance of at least one meter. In addition, make wearing of nose mask a must in the company of people in a commonplace. In addition, meet people outside rather than in 3Cs (places that are closed, crowded, or involve close contact)[63].

All over the world, along with WHO, the majority of the nations supported and imposed a severe lockdown at an early stage of COVID-19 because it is thought to be one of the best and most effective methods for controlling the current outbreak; it could prove to be beneficial if carried out with integrity[64]. Authorities in various countries announced two weeks and then three weeks' lockdown, respectively, which was decided to extend due to the increased number of cases. The lockdown decision was not easy for the governments because it was supposed to affect the economy and the public badly. Along with major issues, the general public also faced sleep disturbance problems, anxiety, and depression due to lockdown[65].

While the majority of cases result in mild symptoms, some progress to acute injury to the lower respiratory tract and pneumonia. Elderly people and people of all ages who suffer from serious health conditions, such as heart disease, lung disease, and diabetes, are at a high risk of death from COVID-19. Common symptoms of the virus include inflammation of the upper respiratory tract and symptoms similar to the flu, such as sneezing, coughing, sinus obstruction, and mucous secretions from the no[66]. After that, the temperature seems to rise to approximately 39 degrees or more during days 7–10, and then the person may feel a partial improvement until the end of the 2-wk period[67].

The COVID-19 pandemic has led to a dramatic loss of human life worldwide and presents an unprecedented challenge to public health, food systems and the world of work[68]. The economic and social disruption caused by the pandemic is devastating: tens of millions of people are at risk of falling into extreme poverty, while the number of undernourished people, currently estimated at nearly 690 million, could increase by up to 132 million by the end of the year[69]. Bereavement, isolation, loss of income and fear are triggering mental health conditions or exacerbating existing ones. Many people may be facing increased levels of alcohol and drug use, insomnia, and anxiety[70]. Meanwhile, COVID-19 itself can lead to neurological and mental complications, such as delirium, agitation, and stroke. People with pre-existing mental, neurological or substance use disorders are also more vulnerable to SARS-CoV-2 infection they may stand a higher risk of severe outcomes and even death[71]. Adherence to preventive measures is the only means to tackle the virus. Reluctance to do so has been reported to be a major problem everywhere. Community's risk perception and poor adherence to COVID-19 mitigation measures remains a major problem. A significant proportion of communities did not perceive the virus as a risk for health. People also think that it originated from a laboratory, and mostly causes mild symptoms, and affects the elderly[72].

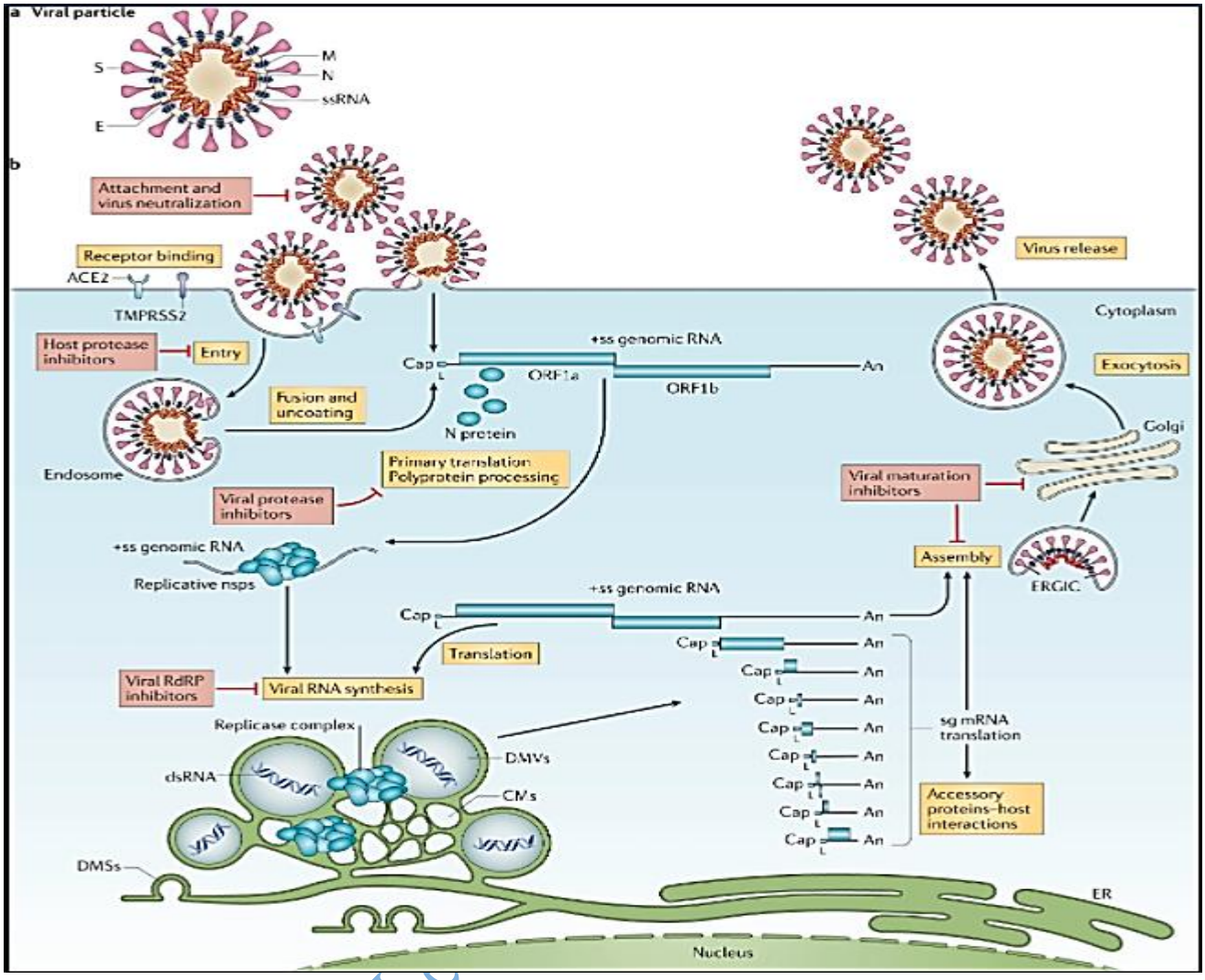


Figure 2.3: Coronavirus Replication

Source[73]

2.6 Epidemiology of COVID-19

Covid-19 was first reported in Wuhan, China in December 2019, where hospitals reported a cluster of spontaneous pneumonia cases with unknown cause. In no time it spread all over the world and the World Health Organization (WHO) declared a state of public health emergency of global concern by 30th January, 2020[73]. The World Health Organization (WHO), (2020), reported that there are two ways in which COVID-19 infection can manifest in the body of the infected people. They can either be asymptomatic or symptomatic, with symptoms disease ranging from fever, cough, respiratory symptoms, shortness of breath, and breathing difficulties[74]. This disease can also have fatal outcome if those symptoms persists and the infected persons has some medical complications especially the one related to respiratory tracts. The fatal outcomes can also include lower-respiratory tract illnesses, such as pneumonia and bronchitis, or acute respiratory distress syndrome (ARDs) and severe acute respiratory syndrome (SARS) in severe diseases. These complications are more pronounced in patients with underlying health conditions such as cardiopulmonary disease, immuno-compromised individuals, infants and the elderly[75].

Globally, the number of confirmed cases has crossed the threshold of 112 million as at 25th February 2021 and caused more than 2.49 million deaths, with United States of America leading the number of confirmed cases with more than 28.3 million confirmed cases and more than 500,000 deaths. In Nigeria, the total confirmed cases were 153,843 as at 25th February, with 1885 total deaths[76].

Epidemiological investigations have shown the incubation period of the SARS-CoV-2 to be between 1-14 days and the virus has also been found to be contagious in the asymptomatic patients[77]. Infection with COVID-19 is more prominent in the elderly people with underlying diseases, where it clinically manifests in form of fever, cough, malaise and acute respiratory

distress syndrome occurring in few patients, which may eventually lead to death. However, in adults and children the disease is usually presented with mild flu-like illness[78]. The overall mortality rate of COVID-19 is 2% which is much lower than that of the severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Increased respiratory transmission of the disease necessitates the practice of strict respiratory precautions for its prevention[79].

The virus is thought to be of natural animal origin, most likely through spillover infection[80]. There are several theories about where the first case (the so-called patient zero) originated and investigations into the origin of the pandemic are ongoing. Phylogenetics estimates that SARS-CoV-2 arose in October or November 2019. A phylogenetic algorithm analysis suggested that the virus may have been circulating in Guangdong before Wuhan[81]. Evidence suggests that it descends from a coronavirus that infects wild bats, and spread to humans through an intermediary wildlife host. The possibility that the virus was accidentally released from a laboratory is also under increasingly active consideration[82].

There is no clear evidence on whether and how prior exposure to a strain of CoV can produce permanent immunity against the strain species or even cross-immunity for other CoV species[83]. Unlike other respiratory diseases that have a quadratic ("U"-shaped) lethality curve (killing infants and elderly, but sparing adults, presumably because adults have a higher chance to be immune against the infection), SARS-CoV-2 has a lethality that continuously rises with age (sparing children but mostly killing elderly)[84]. The severity and the clinical picture could be even related to the activation of exaggerated immune mechanism, causing uncontrolled inflammation as this has been suspected for SARS and MERS. Hence, there is

uncertainty on the impact of individual immune responses on the severity of SARS-like CoV infections[85].

In Africa, the first case of covid-19 was reported in Egypt earlier in the month of February, a second case was reported in Algeria on the 25th of February 2020. Since Algeria is one of the 47 countries in the WHO African region hence it was regarded as the first case in the WHO African region[86]. On the 28th of February, the Nigeria Centre for Disease Control (NCDC) reported the first case of the coronavirus disease in the country. An Italian citizen working in Nigeria returned from Milan, Italy to Lagos and was confirmed by the Lagos University Teaching Hospital Virology Laboratory[87]. Since that first case was announced, the prevalence of coronavirus has been growing steadily across the country to the point that 139 total number of positive cases announced in the first month of the outbreak in Nigeria, has increased to above 150, 000 after about a year[88].

2.7 Epidemiology of Respiratory Syncytial Virus

First discovered in chimpanzees in 1956, the Human Respiratory Syncytial Virus (HRSV, abbreviated RSV) was later discovered in newborns suffering from severe illness of the lower respiratory tract[89]. It belongs to the genus Pneumovirus and subfamily Pneumovirinae and is a non-segmented negative-sense single-stranded enveloped RNA virus of the Paramyxoviridae family. Since two overlapping open reading frames in the M2 mRNA result in two different matrix proteins, M2-1 and M2-2, its 10 genes encode 11 proteins. The G glycoprotein, the F glycoprotein, and the SH protein are the three proteins that make up the viral envelope[90]. While the SH protein is not necessary for either of these processes, the G protein is involved in host cell attachment, the F protein is in charge of fusion and cell entrance. The RSV virus consists of two non-structural proteins (NSI and NS2) and five other structural proteins, including the large (L) protein, nucleocapsid (N), phosphoprotein (P), matrix (M), and M2-

1[91]. It is currently uncertain whether M2-2 also makes up the fully developed virus particles (fig.1).

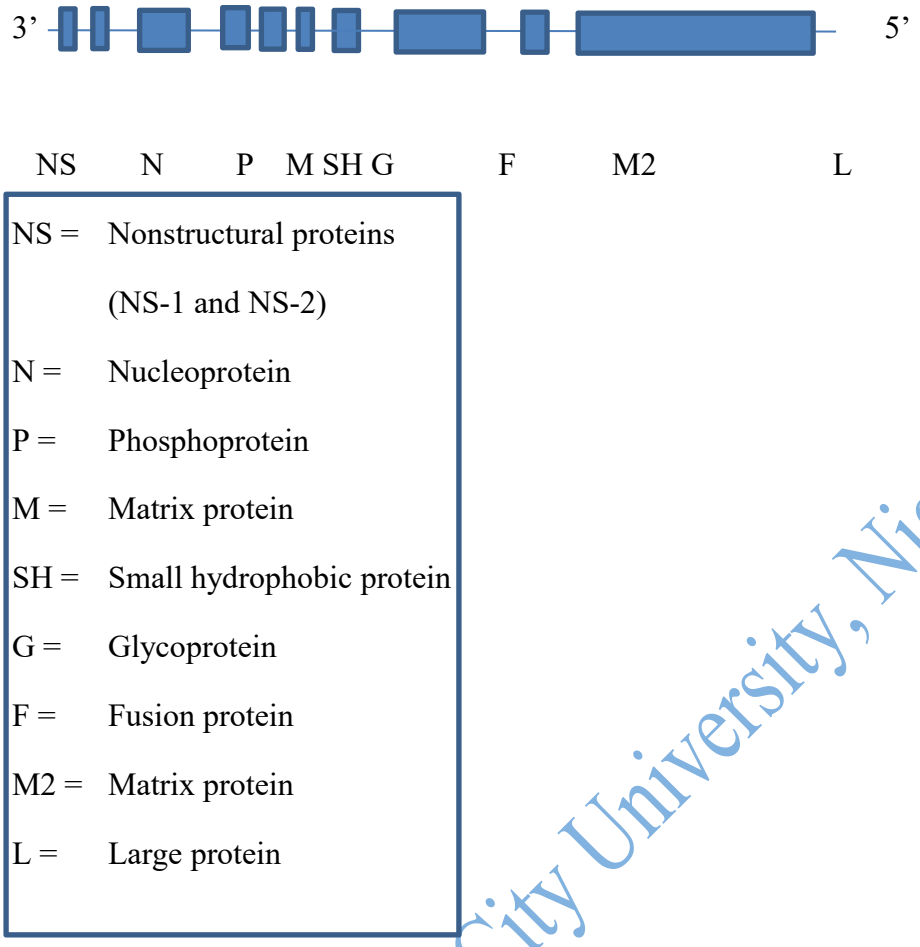


Figure 2.4: The Genetic Structure of RSV

Source[92]

Nearly all children in the United States will have contracted the virus by the time they are 2 to 3 years old, with 60% of infants becoming infected during their first HRSV season. 2-3% of RSV patients suffer from bronchiolitis, demanding hospitalization[92]. People can become infected several times due to the protective immunity that is brought on by a natural RSV infection waning with time, possibly more so than with other respiratory viral infections. Even within a single hRSV season, a baby may occasionally get more than one symptomatic infection[93]. Elderly patients are increasingly being diagnosed with severe hRSV infections. Young adults can be re-infected every five to seven years, with symptoms looking like a sinus infection or a cold (infections can also be asymptomatic)[94].

2.7.1 Structure

The linear negative-sense RNA genome of the human respiratory syncytial virus (HRSV) is found in a medium-sized (120–200mm) envelope virus and must be transformed to a positive RNA before translation. F, G, and SH lipoproteins with viral encoding are present in the first[95]. Only the F and G lipoproteins, which are present in all RSV isolates, are directed at the cell membrane. Based on the virus's reactivity with monoclonal antibodies against the attachment (g) and fusion (F) (5) glycoproteins, HRSV is classified into two antigenic subgroups, A and B[96]. The greater part of the population is affected by asymptomatic strains of the virus, which are referred to as subtype B. Subtype A strains are responsible for the more serious clinical symptoms, and they frequently predominate in outbreaks[97].

Four viral genes-N (nucleoprotein), P (phosphoprotein), M (matrix protein), and L ("large" protein, containing the RNA polymerase catalytic motifs) code for intracellular proteins that are essential for genome transcription, replication, and particle budding[98].The nucleocapsid, which is made up of the RSV genomic RNA and the N protein, serves as a template for the viral polymerase complex to synthesize RNA[99]. A decametric, annular ribonucleoprotein

complex comprising the RSV nucleoprotein (N) coupled to RNA has been crystallized in three dimensions at 3.3A resolution. The viral helical nucleocapsid complex's first turn is mimicked by this complex. Using information from electron microscopy and its crystal structure, a thorough model of the RSV nucleocapsid was created[100].

2.7.2 Genome

The genome has about 15,000bp (base pair) and 11 genes encoding for nonstructural protein 1 (NS1) and (NS2), Nucleocapsid protein Phosphoprotein (P) composed of a single strand of RNA with negative polarity. It has 10 genes encoding 11 proteins[6] to date, 10 HRSV-A genotypes have been designated, GA1 to GA7, SAA1, NA1, and NA2. The HRSV-B genotypes include GB1 TO GB4, SAB1 TO SAB3, and BA1 TO BA6[6]. The genome takes up residence in the helical nucleocapsid, encoding for 11 different proteins, both structural and non -structural[101].

2.7.3. Evolution

Bayesian estimates of the mutation rates in the subtype A genomes give a mutation rate of 6.47 x 10^{-4} (credible interval: 5.56 x 10^{-4} – 7.38 x 10^{-4}) substitutions/site/year[102]. This is similar to other RNA viruses. The population size has remained constant over the last 70 years and the G protein appears to be the main site of diversifying selection. The most recent common ancestor evolved 1943 (credible interval: 1923-1954)[103]Similar to the previously calculated HRSV-A (1.83 x 10-3) nucleotide substitutions/site/year, the HRSV-B evolutionary rate (1.95 x 10-3 nucleotide substitutions/site/year) is comparable. On the other hand, it seems that wild HRSV-B isolates can tolerate more significant alterations to their attachment G proteins[104]. The strains of subgroup B that are currently in circulation are thought to have had a common ancestor as recently as 1949. It was estimated that the two major subgroups diverged about 350 years ago, or in the middle of

the 17th century[105].Respiratory Syncytial Virus infection has been said to ubiquitous in the world, as it is found all over the world. 33.1 million Episodes of RSV-ALRI, resulted in about 3·2 million hospital admissions, and 59 600 (48 000-74 500) in-hospital deaths in children younger than 5 years[106]. In children younger than 6 months, 1.4 million hospital admissions, and 27 300 in-hospital deaths were due to RSV-ALRI globally in 2015. An overall estimate of RSV-ALRI mortality could be as high as 118 200. Although incidence and mortality varied substantially from year to year in any given population. In a previous study by the same authors in 2005, respiratory syncytial virus (RSV) was associated with 22% of all episodes of (severe) acute lower respiratory infection (ALRI) resulting in 55 000 to 199 000 deaths in children younger than 5 years[107].

The infections caused by RSV are seasonal, peaking predictably in the winter months in temperate climates, and in the hottest months and the rainy season in tropical climates. RSV infection develops annually in 4-5 million children, and more than 125,000 children are admitted per year for RSV-related illness. The burden of RSV infection is not limited to only young children. In United States, it is responsible for 177,000 hospitalizations and 14,000 deaths in elderly ≥ 65 years of age[108].

Studies to analyze RSV seasonality in the five distinct regions of Brazil using time series analysis (wavelet and Fourier series) of the following indicators: monthly positivity of the immunofluorescence reaction for RSV identified by virology surveillance system, and rate of hospitalizations per bronchiolitis and pneumonia due to RSV in children under 5 years old (codes CID-10 JI2.1, J20.5, J21.0 and J21, 9)[109]. A total of 12,501 samples with 11.6% positively for RSV (95% confidence interval 11-22.2), varying between 7.1 and 21.4% in the five Brazilian regions, was analyzed. A strong trend for annual cycles with a stable stationary pattern in the five Brazilian regions was identified through wavelet analysis of the

indicators[110]. The timing of RSV activity by Fourier analysis was similar between the two indicators analyzed and showed regional differences. This study reinforces the importance of adjusting the immunization period for high risk with the monoclonal antibody palivizumab taking into account regional differences in seasonality of RSV[111].

In Brazil, RSV was found in 23.1-42.2% of the infants hospitalized for lower respiratory tract diseases and was associated with 3.6% of the deaths[112]. The lack of data on the role of RSV in the total number of hospitalizations and mortality by lower respiratory tract diseases in children under 5 years, especially in developing countries, complicate the evaluation of the global impact of the disease; therefore, it is difficult to better define the priorities and investments needed for prevention and treatment. In Brazil, regional incidence specialties in the seasonality of viral circulation were identified in the south (Porto Alegre), Southeast (Sao Paulo), Northeast (Fortaleza) and North (Belem)[113].

In Nigeria, amongst children utilizing Ibadan's primary and secondary healthcare facilities, the prevalence of RSV was reported to be 34.6%. Both subtypes of HRSV were detected (co-circulating) among the study group. None of the children was co-infected with HRSV A and B, overall. Higher disease severity scores were associated with HRSV-A infection than infection with HRSV-B[114]. In another study, the prevalence of RSV infection was 34.2% and its peak was in the rainy months[115].

2.8 The Metabolic Cycle of Viruses

The fusion of the respiratory syncytial virus with the plasma membrane allows it to enter the cell. The G protein of the RSV binds to a specific long, unbranched polysaccharide of the extracellular matrix made up of disaccharide subunits known as GAGs during the initiation step. GAGs frequently have a role in how different viruses and cells interact[116]. The F protein then engages in an interaction with the RhoA protein to facilitate the virus's attachment.

RhoA's precise function is uncertain, however it may serve as a receptor for the fusion protein or contribute to viral infection. In the cytoplasm, viral gene expression and replication take place. The nucleocapsid and genome of the virus are released once it has entered the cytoplasm. The genomic RNA manufacturing process is controlled by the M2-2 gene from transcription to production[117]. The genes are subsequently translated into mRNAs by the start-stop-restart synthesis once the polymerase enters the genome at its 3 end. As a result, there is a polar transcription gradient, in which the genes upstream of the promoter are transcribed more frequently than the upstream genes. The antigenome, which serves as a template for genome synthesis, is created during replication from the entire positive-sense RNA complement of the genome. The N protein, which serves as the template for RNA synthesis, is constantly coated on both the genome and the antigenome[118] by interacting with the nucleocapsid proteins N, P, and M2-1 as well as the envelope proteins F and G, the M protein controls the assembly of the RSV. The newly synthesized proteins then begin to self-assemble and budding also takes place, obtaining a membrane-derived envelope.

2.9 Signs and Symptoms of RSV

Signs and symptoms of RSV infection most commonly appear about four to six days after exposure to the virus. In adults and older children, RSV usually causes mild cold-like signs and symptoms[119].

These may include:

- Congested or runny nose
- Dry cough
- Low-grade fever
- Sore throat
- Sneezing
- Headache

In Severe Cases

RSV infection can spread to the lower respiratory tract, causing pneumonia or bronchiolitis-inflammation of the small airway passages entering the lungs. Signs and symptoms may include:

- Fever
- Severe cough
- Wheezing - a high-pitched noise that's usually heard on breathing out (exhaling)
- Rapid breathing or difficulty breathing-the person may prefer to sit up rather than lie down
- Bluish color of the skin due to lack of oxygen (cyanosis)

Infants are most severely affected by RSV.

Signs and symptoms of severe RSV infection in infants include:

- Short, shallow and rapid breathing
- Struggling to breathe - chest muscles and skin pull inward with each breath
- Cough
- Poor feeding
- Unusual tiredness (lethargy)
- Irritability

Most children and adults recover in one to two weeks, although some might have repeated wheezing. Severe or life-threatening infection requiring a hospital stay may occur in premature infants or in anyone who has chronic heart or lung problems[120].

Usually 2-8 days after exposure, the illness starts with a runny nose and loss of appetite. One to three days later, fever, coughing, and sneeze may appear. There may also be wheezing[121].

The most common signs of infection in very young infants may be irritability, a decline in activity, and breathing issues. Most infants with RSV infection who are otherwise healthy do not need to be hospitalized. The majority of the time, especially in patients who require hospitalization, full recovery from illness happens in between one and two weeks[122]. RSV infections frequently result in appointments with the doctor. During these visits, the healthcare professional will evaluate the disease's severity to decide whether the patient needs to be hospitalized. Infants may need more oxygen, suctioning of mucus from the airways, or intubation (having breathing tubes put) with mechanical ventilation in the most severe cases of disease[123]. RSV infections in premature babies, infants, and kids with diseases that affect the lungs, heart, or immune system, can lead to other, more serious illnesses such as pneumonia or bronchiolitis[124].

2.10 Contagious Nature of Respiratory Syncytial Virus

Respiratory syncytial virus is highly contagious. It spreads through droplets containing the virus when someone coughs or sneezes[125]. It also can live on surfaces (like counters or doorknobs) and on hands and clothing. So people can get it if they touch something that's contaminated. RSV can spread quickly through schools and childcare centers. Babies often get it when older kids carry the virus home from school and pass it to them[126]. Almost all kids have had RSV at least once by the time they are 2 years old. RSV infections often happen in epidemics that last from late fall through early spring. Respiratory illness caused by RSV-such as bronchiolitis or pneumonia-usually lasts about a week, but some cases may last several weeks[127].

Risk Factor for RSV

- Premature babies
- Older adults, especially those 65 years and older
- People with chronic lung disease or certain heart problems
- People with weakened immune systems, such as from HIV infections, organ transplants, or specific medical treatments like chemotherapy

Bronchiolitis

Bronchiolitis is a lower respiratory tract infection that can result from RSV. It commonly affects those under 2 years old.

The airways become inflamed and infected. The following symptoms may occur:

- Fever
- Dry, persistent cough
- Feeding problems
- Wheezing

Most cases are not serious, but if the child has difficulty breathing or feeding, if they have a high temperature, or if they seem tired or irritable, you should call a doctor[128].

Hospitalization of RSV Infection

Early birth perinatal chronic lung disease (perinatal CLD) congenital heart disease (CHD) with hemodynamic significance birth weight below the 10th percentile, in particular, Congenital or acquired immunodeficiency in infants. Down syndrome (trisomy 21) and other chromosomal anomalies or malformations Idiopathic pulmonary disease Muscular dystrophy liver illness Inborn metabolic mistakes Preterm birth, chronic lung disease (CLD) of prematurity, and hemodynamically severe congenital heart disease (CHD) are well-established host risk factors

for hospitalizations.). Low birth weight is another risk factor for RSV hospitalizations, specifically birth weight below the 10th percentile[129]. Infants with inherited or acquired immunodeficiencies are also susceptible to life-threatening illness. Trisomy 21 (Down syndrome), other chromosomal abnormalities, malformations, neuromuscular disease, liver disease, and inborn errors of metabolism have also been linked to a double fold increased risk of hospitalization as a whole, with individual frequency ratios spanning from 1.5 for encephalocele to 4.3 for cystic fibrosis [130]. Prematurity of birth and underlying medical conditions raise the risk of hospitalization as well as of clinical disease manifestations that are more severe, as shown by a higher frequency of the need for mechanical ventilation, admission to the ICU, lengthier hospital stays, and higher mortality rates[131].

Even though the aforementioned risk factors increase the likelihood of hospitalization, at least half of all newborns hospitalized for RSV infection were previously healthy and did not have any of these known medical risk factors[131].Young age (6 weeks to 6 months), male sex, siblings or other children living in the home, especially when they are older than the index child and already attending daycare or school, the infant's attendance at daycare, exposure to environmental tobacco smoke, particularly maternal smoking during pregnancy and lactation, as well as male gender are the most frequently and consistently identified risk factors in this group[132].

2.11 Neuromuscular Disease

There was a significant difference in the attributable mortality between children with neuromuscular disease and controls (5.5% versus 0.2%). Similarly, an observational study confirmed that infants between 29- and 32-weeks' GA with neurological disease were twice as likely to require prehospitalization with RSV as were preterm infants without impairment[133]. The study involved 1541 patients across 14 pediatric hospitals in Germany who were

hospitalized at a median age of 14 months. Children with neuromuscular impairments had a nine-fold increased risk of seizures with a five-fold increased risk for ventilation compared with the control group[134].

2.12 Infants with Down Syndrome

A few risk factors that increase the likelihood of adverse outcomes for infants with Down syndrome if they contract RSV include relative hypotonia, congenital cardiac disease, mid-face hypoplasia with smaller airways, pulmonary abnormalities with a decreased total number of alveoli and corresponding alveolar surface area, increased risk of pulmonary hypertension, and imbalances and alterations in cellular and humoral immunity[135]. Infants with Down syndrome who are born without a cardiac defect are more likely to be admitted to the hospital before turning two years old with RSV (overall incidence 7.6% versus 0.7% in sibling controls); this risk rises to 11.9% when there is substantial heart disease [136,137].

2.12.1 Cystic Fibrosis

Individuals with cystic fibrosis (CF) experience recurrent flare-ups of pulmonary infection and inflammation with a startling tendency for Pseudomonas species colonization of the airways. Using fluorescence cytometric assays, it was shown that Pseudomonas species adhered to epithelial cells more readily in vitro when RSV infection had already occurred and more strongly in cell monolayers when RSV was added concurrently. RSV is thought to encourage pseudomonal attachment to RSV glycoprotein G, according to the authors. RSV infections are more common in CF patients under the age of two who also have chronic[138].

2.12.2 Immunodeficiency

Immunocompromised children, especially those with cell-mediated immune abnormalities, have higher rates of morbidity and mortality (varying from 1.7% to 40%, extended viral shedding, and greater illness severity during lengthy hospital stays. They also have trouble clearing RSV infection[139].

2.12.3 Aboriginal Children

Rates of LRTI in Inuit and First Nations children are generally several fold higher than their non-aboriginal counterparts[140]. RSV-specific admission rates for Inuit infants of all GAs are 166/1000 infant-years on Baffin Island (Nunavut) and 328/1000 to 512/1000 infant-years for infants younger than six months of age living in remote communities. RSV admission rates for preterm and term Alaska Native infants from the Yukon Delta are 317/1 000 and 1-78/1 000, in comparison to the average of 25/1000 to 30/1000 US children, respectively. Exposure to smoke, smoking while pregnant, a lack of access to health care, poverty, crowded living conditions, prematurity and younger ages, adoption, discontinuation of breastfeeding, and perhaps a genetic predisposition are risk factors that have been linked to this demographic globally[141].

2.13 Total Burden of RSV Infections

The total burden and hospitalization rates for RSV-associated respiratory infections are difficult to estimate because routine testing to determine the viral etiology is not performed in an outpatient setting and is not even recommended for hospitalized cases in US guidelines because the results of virology would not affect management[142]. RSV is estimated to have caused 33.8 million episodes of acute LRT1, 3.4 million episodes of severe acute LRTI requiring hospitalization, and at least 66,000 deaths in children under the age of five globally, with the majority of severe cases and fatalities occurring in children under the age of two and fatalities being significantly more common in developing countries. These estimates are based on data from published and unpublished studies with widely varying methodologies[143]. There

is a lot of variety in the reported hospitalization rates, but it's not apparent yet whether this is primarily due to methodological variations or actually reflects regional differences in the frequency of severe RSV infections.

Population-based active surveillance of laboratory-confirmed RSV infections in the US alone has produced estimated hospitalization rates of 17–18.5/1,000 babies under the age of six months and 5.1–7.4/1,000 in infants between the ages of six and eleven months for the years 2000–2004[144]. Children under the age of five had an overall rate of 3/1,000 to assess rates against those reported from other industrialized nations). The rates for visits to the emergency room and pediatric doctors' offices linked to RSV infections were 28/1,000 and 80/1,000, respectively, in the same study[145]. Take note that all of these rates varied significantly both annually and regionally. Extrapolated to the full US population, it is projected that 2.1 million children under the age of five need medical care each year for RSV infection, with 3% of them being admitted to hospitals, 25% receiving care in emergency rooms, and 73% visiting pediatric offices. The fact that over two thirds (61%) of outpatient visits involve children between the ages of 2 and 5 and that more than three quarters (78%) of patients requiring medical care for RSV infections are older than 1 year is particularly significant[146].

RSV-associated hospitalization rates have been somewhat elevated, with estimates ranging from 23.4 to 27.4/1,000 in infants less than 1 year from hospital discharge data[147]. Infants under 6 months old had frequencies that were significantly higher (44.5/1,000 live births) than infants between 6 and 11 months (24.2/1,000)[148]. For the years 1997 to 2006, according to another investigation, the rates for infants aged 0 to 2 months were 48.9, those aged 3 to 5 months were 28.4, and those aged 6 to 11 months were 13.4. The highest frequencies were observed in Native infants residing in Alaska and the Southwest, with rates of 70.9 and 48.2 per 1,000 for RSV hospitalizations, respectively. This is particularly noteworthy because American Indian

and Alaska Native infants are hospitalized much more frequently due to RSV infection than the general US infant population[149]. Hospitalization rates for RSV bronchiolitis and pneumonia, when broken down by type of illness, were 24.2 and 3.0 per 1,000 births, respectively. For newborns of American Indian and Alaska Native descent, the equivalent rates of bronchiolitis were 54.54 and 43.4 per 1,000, respectively. Given that the aforementioned data pertain to the years 2000–2001, when RSV hospitalization rates in the Yukon Delta were found to be the lowest recorded between 1994 and 2004[150], at least for Alaska Native newborns, this appears to reflect a considerable underestimating of the typical yearly hospitalization rates. The overall frequency was 178/1,000 from 1994 to 1997, and it dropped to 104/1,000 from 2001 to 2004 partly because fewer premature high-risk newborns were admitted to the hospital with RSV following the introduction of Palivizumab treatment. Additionally, extremely high rates of hospitalization for bronchiolitis, particularly RSV bronchiolitis have been observed in Canadian Inuit newborns[151].

Although more recent data indicate a proportion of 19.5%, bronchiolitis of any origin accounted for 16.4% of hospitalizations in infants under 1 year of age in the US in 1996 (an increase of around three times compared to 1980)[152]. Bronchitis is the discharge diagnosis in 45-85% of RSV hospitalizations, with some of the highest percentages coming from recent US surveillance and hospital discharge data. On the other hand, RSV is the cause of 50–80% of bronchiolitis hospitalizations. More particular, RSV makes up 70-75% of the virus-positive samples[153], and a virus is detected by (RT)-PCR in 75-95% of infants under 2 years' old who are hospitalized with bronchiolitis. It's interesting to note that the proportion of RSV does not significantly change depending on whether sampling is done across a number of years, a single full year, or simply during one or more RSV seasons[19]. This clearly demonstrates that RSV is the most common reason for bronchiolitis hospitalizations, but it also emphasizes that other viruses, such as rhinovirus, hMPV, corona, parainfluenza, and influenza viruses, boca virus,

and AdV, can cause bronchiolitis.[154]. In patients with RSV, hMPV, or rhinovirus infections, the proportion of patients with a discharge diagnostic of bronchiolitis is comparable. Although some data suggest that picornaviruses, including rhinovirus, are the most frequent etiological agent in acute respiratory illnesses requiring hospitalization even in this population, the overall hospitalization rates for these viruses generally are significantly lower than RSV-associated disease in infants 1 year of age[155]. The most common cause of acute respiratory illness and LRTI in general, according to prospective community-based studies from Wisconsin, Western Australia, and the UK, is now rhinovirus; in contrast, RSV is still the most common viral agent in LRTI, especially bronchiolitis severe enough to require hospitalizations.1.2 Atopy has been connected to rhinovirus-associated wheezy respiratory tract disease, and children in two of these groups were at increased risk of acquiring it[156]. As a result, these cohorts might not accurately reflect the general population. However, picornaviruses (which include rhinovirus) were also found to be the most common cause of acute respiratory episodes, including LRTI in unselected cohorts[157].

2.14 Diagnosis of RSV

In clinical pediatric practice, rapid confirmation of RSV infection in the lab leads to a decrease in the need for auxiliary testing, a reduction in the usage of antibiotics, and shorter hospital stay[158]. In order to rule out alternative causes and prevent delayed diagnosis, laboratory diagnosis is especially necessary for children with atypical clinical presentations, such as respiratory distress or sepsis-like syndrome, and in premature newborns with non-specific symptoms[159]. It is crucial to quickly identify infants who are affected in hospital wards in order to implement the proper infection control measures and stop nosocomial outbreaks since RSV is contagious. In order to be proactive for preventative programs and to

evaluate the effectiveness of antiviral prophylaxis[160]. There are further justifications for viral testing, such as research and epidemiological RSV activity monitoring[161].

Co-infection of RSV

RSV and Influenza A and B

Influenza A virus (IAV) is a pathogen that causes the flu in birds and some mammals, including humans[162]. It is an RNA virus whose subtypes have been isolated from wild birds. Occasionally, it is transmitted from wild to domestic birds, and this may cause severe disease, outbreaks, or human influenza pandemics. Each virus subtype has mutated into a variety of strains with differing pathogenic profiles; some may cause disease only in one species but others to multiple ones. A filtered and purified influenza A vaccine for humans has been developed and many countries have stockpiled it to allow a quick administration to the population in the event of an avian influenza pandemic[163]. Influenza B virus is known only to infect humans, pigs and seals. This limited host range is apparently responsible for the lack of associated influenza pandemics in contrast with those caused by the morphologically similar influenza A virus as both mutate by both antigenic drift and re-assortment[164]. There are two known circulating lineages of influenza B virus based on the antigenic properties of the surface glycoprotein hemagglutinin. The quadrivalent influenza vaccine licensed by the CDC is currently designed to protect against both co-circulating lineages and has been shown to have greater effectiveness in prevention of influenza caused by Influenza B virus than the previous trivalent vaccine[165].

Respiratory viral infections are caused by a diverse group of viruses, including influenza A and B viruses (IAV and IBV), severe acute respiratory syndrome virus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), and human rhinovirus (HRV)[166]. Respiratory syncytial virus (RSV) and influenza viruses are two respiratory viruses associated with significant morbidity and mortality worldwide. RSV is a leading pathogen causing acute lower respiratory tract infection (ALRTI) in all age groups, primarily infants and young toddlers,

while the influenza virus affects all age groups. The activity of both innate and adaptive immune systems against both viruses is very well documented. Innate immunity against these viruses includes, among others, the interferon-stimulating gene (ISG) pathway, which triggers the expression of the interferon-induced protein with the tetratricopeptide (IFIT) family of proteins[167].

In humans, IFIT1–3 proteins form a complex with each other to inhibit translation of viral mRNA molecules. IFIT1 acts as a sensor that identifies specific viral single-stranded RNAs and selectively inhibits viral protein synthesis without affecting host cell protein synthesis[168,169]. While IFIT1 is known to specifically recognize the viral mRNA, it has been suggested that IFIT2 and IFIT3 facilitate the binding of the IFIT1: complex structure to the viral mRNA. IFI44 is also an ISG and its expression is induced following infection with different viruses. However, less is known about IFI44 function against these viruses. In influenza virus-infected cells, IFI44 is upregulated and was found to regulate the innate immune responses by negatively modulating interferon response pathways to control exacerbated immune reaction[170].

2.14.1 Laboratory Diagnosis of RSV

The identification of the virus, viral antigens, or virus-specific nucleic acid sequences in respiratory secretions allows for the precise diagnosis of RSV infection. The sensitivity and specificity of all currently available viral detection tests are significantly influenced by the kind and quality of the clinical specimen[171]. It has been shown that compared to a nasopharyngeal swab specimen, a nasal wash or nasopharyngeal aspirate is more sensitive in detecting RSV. But taking a nasopharyngeal swab is much less painful for the patient, doesn't require any specific tools, and may be done in an outpatient environment[172]. Utilizing the recently developed flocked-nasopharyngeal-swabs, which efficiently loosen and gather virus-

infected cells lining the nasopharynx, considerably enhances the swab specimen quality and boosts the clinical specimen's diagnostic yield[173]. Currently available laboratory methods for the detection of RSV include tissue culture virus isolation, detection of viral antigens by enzyme-linked immunosorbent assays (EIAs) or direct or indirect immunofluorescent staining (DFA/IFA), and detection of viral nucleic acids by amplification assays, primarily reverse transcription polymerase chain reaction (RT-PCR)[174] .

Respiratory Syncytial virus primary infection is thought to be almost always symptomatic, although statistics point to the possibility that this may not be the case[175]. From a minor infection of the upper respiratory tract (URTI) or Otitis media to a serious and potentially fatal lower respiratory tract involvement (LRTI), there are a variety of clinical symptoms. Bronchiolitis is the most typical LRTI in newborns with RSV infection, but pneumonia and croup are also prevalent. Babies between the ages of 2 and 6 months are most at risk for involvement of the lower airways, which occurs in 15–50% of babies and young children with initial RSV infection and needs hospitalization in 1-3% of the annual birth cohort [176.] However, in other areas, infants between the ages of 6 and 11 months or even kids between the ages of 1 and 2 are known to have the highest prevalence of LRTI. In ~5-10 % of hospitalized newborns, the condition is severe enough to need admission to the intensive care unit (ICU). newborns born in developed nations who were previously healthy have few deaths, but newborns and children from developing nations and people with chronic diseases like heart disease or lung disease have considerably higher mortality rates[177.]

RSV reinfections are seen in 30–75% of children under the age of two who had an infection during the first year of life, and they typically happen during the following season[169]. The severity of the epidemic determines the rate of reinfection once more. The disease is typically symptomatic in young children, even in secondary infections, but the severity gradually lessens

with repeated exposures, with fewer kids reporting fever, middle-ear effusions, or bronchiolitis or other lower respiratory illnesses[178]. RSV is a major cause of morbidity and mortality in these populations, accounting for bronchitis and wheezing in around 25% of symptomatic elderly and frail people[179]. Nonetheless, individuals with impaired immune systems, chronic cardiac conditions, and tracheobronchitis are also susceptible to a significant involvement of the lower respiratory tract. Although reinfections are still common throughout life, LRTI symptoms are typically absent or limited to the upper respiratory tract in older children and adults.

Bronchitis is the most typical symptom of RSV LRTI, although there is no consensus on how to define this condition. The phrase is most frequently used to describe an acute viral LRTI in children or babies under the age of 24 months that starts with rhinorrhea and progresses to a dry, wheezy cough, tachypnea, dyspnea, and frequently subcostal, intercostal, and supraclavicular retractions[180]. There may be a fever, but a high fever is unusual. Very young and preterm newborns may exhibit apnea. On auscultation, these clinical symptoms are accompanied by wheezing and/or fine inspiratory crackles. While numerous crepitations are regarded as the hallmark of bronchiolitis in the United Kingdom, Australia, and other parts of Europe, only wheezing would be classified as induced wheeze caused by virus in North America and certain regions of Europe. Some medical professionals advise restricting the diagnosis of bronchiolitis to the first wheezing episode[181].

Acute bronchiolitis is diagnosed clinically based on the presence of the normal respiratory symptoms, which may also include tiredness, irritability, and poor food intake. The hyperinflation and patchy atelectasis may be visible on a chest X-ray. Although X-ray results may be useful in distinguishing between pneumonia and bronchiolitis, X-rays are not always necessary and should only be used in cases of diagnostic uncertainty[182]. It should be noted that a lot of epidemiological studies, especially those from developing nations, now refer to any RSV LRTI as pneumonia

because bronchiolitis and pneumonia are hard to tell apart clinically or radiographically. Although routine use is not advised due to the minimal risk of dangerous bacterial infections in infants with bronchiolitis, even if they are febrile, bacteriological testing may be beneficial in cases of diagnostic ambiguity[183]. When a patient is admitted to the intensive care unit (ICU), the risk of bacterial infection increases. Although experts dispute on whether supplementary oxygen should be started at an oxygen saturation of 92 or 90%, pulse oximetry is advised for all patients arriving to the emergency room. Even though some advocate routine rapid antigen testing for RSV to direct cohort arrangements, the American Academy of Pediatrics (AAP) guidelines do not advocate routine virological testing because the results of such tests rarely change management choices but do find it to be helpful when cohorting is desired[184].

While RSV infection can still be confirmed by viral culture, direct or indirect immunofluorescence, ELISA, and antigen detection are not universally available for all respiratory viruses[185]. Reverse transcription-polymerase chain reaction (RT-PCR) for RNA viruses and polymerase chain reaction (PCR) for DNA viruses are therefore increasingly used in epidemiological studies to determine the viral etiology. It is the only method for the detection of some recently discovered viruses, such as the human metapneumovirus (hMPV) and Boca viruses, and it has significantly increased the detection frequency of rhinovirus, parainfluenza virus, and adenovirus (AdV)[186]. However, this does not significantly improve the detection frequency of RSV unless it is combined with hybridization. However, there is still disagreement on how to interpret positive RT-PCR results given that a sizable proportion of samples taken from asymptomatic individuals without signs of recent respiratory infections are positive by RT-PCR[187].

2.14.2 Detection of Viruses using Cell Culture

For a very long time, RSV isolation in tissue culture was regarded as the most accurate method for confirming a possible RSV infection. However, this method takes an average of 3

to 6 days before the impact of syncytial cytotoxicity manifests[188]. This is in addition to the technical knowledge in adequate specimen management for optimal viral recovery. The sensitivity of the tissue culture approach is considerably increased by shell vial spinning cultures followed by DFA or immunoperoxidase labeling with virus-specific monoclonal antibodies, which reduces the time required for virus detection to 1 to 2 days[188]. The cell culture method is beneficial because it has a higher sensitivity than rapid antigen detection kits. and also allows for further antigenic and genetic characterization of the amplified virus, which can be used for the detection of epidemiologically significant mutations or for the confirmation of nosocomial spreading by sequencing[189].

2.14.3 Identification of Antigens

Chromatographic and optical immunoassays ,enzyme immunosorbent assays (EIA), direct immunofluorescence assays (DFA), are a few examples of antigen detection assays[190]. The advantage of the DFA is the pattern of immunofluorescence displayed by the infected cells may be directly inspected by microscopy, providing more evidence of specificity. The DFA utilizes fluorescein-labelled antibodies that detect RSV antigen in epithelial cells in respiratory secretions. RSV-specific antibodies will gather any RSV antigen that is present in the EIA, and a second enzyme-linked antibody will identify it[191]. The procedures for antigen testing kits are simple, and the results appear promptly. They are frequently employed in clinical practice due to these factors. In comparison to cell culture, the current kits for detecting antigens for pediatric specimens have sensitivities of 72 to 94% and specificities of 95 to 100%. Nevertheless, detection rates for EIA in older children and adults are incredibly low, with sensitivities ranging from 0 to 20%. This is most likely due to significantly lower viral titre and shorter virus shedding in a categories of patients with RSV reinfections[192]. Antigen detection kits' specificity can be greatly decreased, particularly if they are used

outside of epidemic times when the virus is less common in the community and the false positive rate is higher. Nucleic acid amplification assays are more sensitive and specific than other approaches, despite several attempts to increase the sensitivity and specificity of antigen detection kits[193].

2.14.4 Tests on Nucleic Acids

Regardless of the patient group studied, nucleic acid assays have completely transformed the diagnostic processes in virology and are the most sensitive and specific approaches for RSV identification. Research comparing nucleic acid testing to viral isolation in cell culture and to antigen detection techniques have shown improved sensitivity, which increases detection rates for children with respiratory illnesses by around a factor of two[194]. When a young child has an initial infection, they typically shed a lot of RSV over an extended period of time. Due to the presence of secretory and humoral virus-specific antibodies, which influence the level of viral replication, virus is shed in lesser quantities for shorter periods of time with an increasing number of recurrent infections. As a result, many investigations have noted a decline in the effectiveness of RSV detection with increasing patient age. However, due to the reduced virus generation in elderly patients, molecular diagnostic techniques are unquestionably also more sensitive for older age groups[195].

Ag-ELISA, semi-nested RT-PCR, and virus isolation with consideration for the patient's age are used to detect the respiratory syncytial virus in NPAs. The reverse transcription polymerase chain reaction (RT-PCR) was the first and most widely utilized nucleic acid-based assay among the several nucleic acid amplification methods. The RSV genome has been amplified using multiple internal PCR techniques over the past ten years, and an increasing number of commercial RSV NAT kits are also currently easily accessible[196].

Real-time PCR procedures, for instance, are one of the new PCR techniques that have been created. The simultaneous performance of amplification and detection is made possible by real-time PCR assays that use fluorescent probes like Taqman, molecular beacons, and scorpion probes, which significantly speed up RT-PCR and have a turnaround time of just a few hours[197]. Additionally, protocols have been developed for the simultaneous amplification of RSV and a number of other respiratory viruses that exhibit comparable clinical symptoms.Multiplex PCR methods like these may detect numerous respiratory viruses concurrently, either in parallel detection in a single PCR cycle or within a single tube. It was discovered that up to 50% of RSV infections in newborns and up to 10%–30% of respiratory disease patients constitute mixed infections of two or more respiratory viruses using very sensitive monoplex or multiplex PCR techniques. There is ongoing debate regarding how a coinfection affects the clinical course of the condition. Some research have found that the identification of two respiratory viruses compared to one has a considerably higher risk of more severe illness or admission to a pediatric intensive care unit, but other studies have found the opposite to be true[198].

Real-time PCR's ability to quantify viral nucleic acids in a sample is a significant advantage. Because respiratory specimens cannot easily be standardize, particularly in regards to the quantity of virus or virus-infected cells within specimens and the non-standardized dilution of samples[199], When it comes to respiratory tract infections, the diagnostic utility of determining viral loads is still unresolved. In terms of RSV, greater viral loads appear to be associated with a more severe clinical course of the illness and an increased risk of wheezing recurrence. Quantitative RT-PCR may be used to distinguish between the virus that is truly causing an acute respiratory sickness in a patient and viruses that are simultaneously detected but do not have a direct link to the clinical symptoms[200].

2.14.5 RSV-Specific Antibody Determination (Serology)

The diagnosis of acute RSV infection cannot be done by testing for virus-specific antibodies. Despite severe Infection with RSV, a serologic reaction is typically not detected in newborns. The infant's own antibody response is hardly detectable in the presence of maternally derived antibodies, repeated infections are usually not associated with a detectable antibody response, even in older children and patient groups, and even with sophisticated testing for the identification of class-specific antibodies. The primary aims of screening for RSV-specific antibodies are seroepidemiologic data gathering and research[201]

2.15 Transmission of RSV

RSV patients typically remain contagious for 3 to 8 days. However, certain young children and those with compromised immune systems may remain contagious for up to four weeks. RSV can spread quickly to other people[202]. RSV can be transferred when an infected person coughs or sneezes into the air and releases droplets containing the virus. These droplets may persist in the air for a short while, and if someone breathes them in or they come into contact with their nose, mouth, or eyes, they may infect them. Direct and indirect contact with nasal or oral secretions from infected people can also cause infection. Kissing a child with the RSV virus on their face, for instance, can result in direct contact with the virus[203]. If the virus gets on a doorknob or other environmental surface and is then touched by other persons, it may cause indirect contact. People typically contract a virus directly or indirectly when they touch an infectious discharge and then rub their eyes or nose. RSV can spend a long time on hard surfaces like bed rails and tables. RSV generally survives for a shorter period of time on soft surfaces like tissues and hands204. RSV infection is spread by coming in contact with big droplets of infected people's nasopharyngeal secretions. The conjunctiva, nose, and mouth mucosal surfaces are where the virus enters the body. It can be spread directly or indirectly

by touch and can persist for up to 7 hours on porous and non porous exteriors similar to plastic toys and clothing[205].

2.15.1 Immune Response to Acute RSV Infection Viral Immune Evasion Mechanisms

RSV re-infections are frequent throughout life, despite the fact that antigenic variation among RSV strains is very low in comparison to other respiratory viruses, suggesting that the immune system's protective response is insufficient and transient. This is at least in part because RSV, like other viruses, has evolved a variety of defense mechanisms to circumvent or trick the host immune response[206]. The G protein is highly glycosylated, which has been found to obstruct antibody recognition. The G protein, along with the F protein, is the sole RSV antigen generating neutralizing antibodies. The ability to manufacture the G protein in both its full-length membrane-bound and shortened secreted forms is another immune evasion strategy. The released protein could confuse antibodies that would otherwise neutralize it[207]. Additionally, the G protein has a CX3C motif in its core conserved region, giving it the capacity to communicate with the CX3CR1 receptor and engage in chemotactic activity akin to that of fractalkine (CX3CL1). It is unclear from the available data whether this affects or improves leukocyte recruitment to the infected lung in vivo[208]. As compared to priming with the F protein, which activates both CD4+ and CD8+ T cells and causes both type 1 cytokines and lung inflammation, sensitizing mice with recombinant vaccinia virus expressing the RSV G protein followed by an RSV challenge activates primarily CD4+ T cells and induces eosinophilia in the context of a Th2-dominated immune response. Interleukin (IL)-4 and IL-10 are also produced by human RSV G protein-specific T-cell lines, but the cytokine profile of F protein-specific T-cell lines is Thl-dominated and comparable to that induced by live virus. This suggests that the RSV G protein may be able to suppress cellular immunological reactions[209]. Additionally, there is evidence that the G protein can inhibit inflammatory responses by opposing signaling via toll-like receptors (TLRs). RSV can also infect dendritic cells (DCs), developing them but reducing their capacity to activate naive T cells and deliver antigen. This alters the cytokine milieu through

a variety of processes. These include the release of an inhibitory factor and the inability of DCs and naive T cells to create an immunological synapse. Additionally, type I IFNs, which are crucial for the removal of the virus, can be inhibited by the NS1 and NS2 proteins of RSV[210].

2.15.2 Undeveloped Infant's Immune System

The first few months of life are when primary RSV infection most frequently occurs. Despite the fact that under some circumstances the immune systems of newborns and early babies can produce responses like those of adults, both innate and adaptive immune responses are frequently marked by quantitative or functional impairments[211]. Neonatal, young infant, and kid macrophages frequently exhibit significantly reduced cytokine output when compared to adult macrophages. This is caused, at least in part, by pathogen-associated pattern recognition receptors' lower expression or their diminished upregulation upon activation**.**

Compared to adults, newborns have less DC and a different distribution of subsets. Due to decreased expression of MHC class I and II and co-stimulatory molecules as well as decreased secretion of cytokines, specifically IL-12p70, they exhibit symptoms of impairment in antigen presentation and T cell stimulation[212]. The most notable aspect of neonatal T cell responses is their remarkable plasticity, which ranges from a relative lack of sensitivity to stimuli that elicit powerful reactions in adult T cells to the ability to produce responses similar to those of adults if and when the right stimuli are presented. However, CD4+ T cells frequently show a decreased capacity to generate both Thl and Th2 cytokines. Specifically, it may take until adolescence for the mitogen-induced and antigen-specific synthesis of interferon (IFN) y to reach adult levels[213]. Although Th2 skewing has been found in newborn mice and in human neonatal responses to environmental allergens, it has not been firmly proven that it occurs in human virus infections

despite this low IFNy-producing capacity. While newborns may occasionally display suboptimal CD8+ T cell responses, it is undeniably true that they are capable of maturing cytotoxic T lymphocyte (CTL) responses to distinctive antigens, including viruses[214].

Although greater antibody titers to specific vaccines have been found in some situations, neonatal B cell antibody production is frequently characterized by delayed initiation, decreased peak liters, and shorter longevity[215]. Additionally, after coming into contact with their corresponding antigen, newborn B cells do not exhibit many somatic hyper mutations, which lowers the affinity and decreases the heterogeneity of the antibody repertoire. The fact that only people who are immunocompromised due to immunodeficiency diseases, chemotherapy, or immunosenescence experience severe lower respiratory tract involvement with RSV infection after the age of 2 years suggests that the immune system's immaturity in early childhood is a significant contributor to the frequent occurrence of LRTI during first RSV infection[216]. The typical human immune response to an initial RSV infection is poorly understood. There are various reasons for this. One reason is that lab confirmation is typically only sought in the most serious conditions that necessitate hospitalization, which may not be indicative of the milder disease encountered in the vast majority of patients. Additionally, because primary RSV infections happen at such a young age, sampling is typically restricted to non-bronchoscopic BAL fluid taken from patients who are mechanically ventilated as well as nasal lavage or nasopharyngeal aspirates (NPA) that are routinely taken for diagnostic or therapeutic purposes. As a result, experimental models provide the majority of the knowledge currently known on the human immune response to RSV infection[217].

RSV infection mostly affects bronchial and bronchiolar ECs, especially ciliated ECs[218]. Immortalized respiratory epithelial cell lines are the most widely used in vitro models for investigating the reactions of airway EC to RSV infection. However, there is mounting proof

that their reactions to an RSV infection differ significantly from those of primary airway ECs. These differences include different viral replication kinetics, lower viral titers, lowered cytotoxic responses, and decreased production of pro-inflammatory cytokines. Additionally, primary respiratory ECs maintain the donor characteristics, i.e., they appear to accurately mimic the range of human sensitivities to RSV infection[219].

The most accurate in vitro model to explore the interaction of RSV with host cells is probably well-differentiated human airway epithelial cultures[220]. When cultured at an air-liquid interface, primary human respiratory ECs develop into polarized pseudostratified airway epithelium that has all the cell types and possesses all the morphological and functional traits of healthy respiratory epithelium, including mucus production, ciliary motion, and cytokine and chemokine production. This model has been utilized to confirm that RSV selectively targets polarized epithelial cells and infects the airway epithelium from the apical side, as was earlier observed in autopsy studies[221]. The virus also starts to budding and release from the apical surface, where it is then propagated by ciliary motion. Patchy infection is the consequence, indicating that not all ciliated cells are vulnerable to RSV infection. It has been shown that this model captures many of the characteristics of severe RSV infection in human infants, including apoptosis and sloughing of ECs, mucus hypersecretion due to goblet cell hyperplasia or metaplasia, and the production of various chemokines and cytokines[222]. However, there is some disagreement regarding the extent of cytopathology induced by RSV infection, including syncytia formation.

Although nucleoli has recently been found as a good candidate the RSV receptor has not yet been identified[223] The early response to RSV is known to be mediated by a number of extracellular and intracellular pattern recognition receptors, including TLRs 2, 3, 4, and 7, RNA helicases, including retinoic acid-inducible gene I, and possibly nucleotide-binding oligomerization domain-like

receptors[224]. Airway ECs can produce a variety of cytokines and chemokines, including macrophage inflammatory protein-la (MlP-la, CCL3), monocyte chemo-tactic protein-1 (MCP-1, CCL2), RANTES (regulated on activation, normally T cell-expressed and secreted, CCL5), eotaxin (CCL11), IL-8 (CXCL8), monokine induced by IFNy (M1G, CXCL9), l.P-10 (CXCL10), fractalkine (CX3CL1), but also the proinflammatory cytokines IL-1/3, IL-6, and TNFa, upon infection in Vitro[218]. Regarding the ability of RSV to trigger airway ECs' production of the antiviral cytokine IFN, contradictory results have been found. The differences in the results could be attributed to the use of epithelial cell lines rather than primary human ECs, which have varied reactions to infection with the same RSV variant. Epithelial cells from different donors exhibit significant variation in their cytokine and chemokine responses to infection with the same RSV strain, and both constitutive production and upregulation following RSV infection depend on the location of the epithelial cells in the airways[225]. Individual strains of RSV also differ significantly in their capacity to induce some of these cytokines and chemokines. Alveolar macrophages have the ability to increase the release of chemokines and cytokines from bronchial ECs as well as to contribute to their production, either in response to a brief infection or in response to activating signals received from these cells. There are numerous recombinant hosts used in animal models of human RSV illness, however they are only moderately receptive to hRSV infection[226] They include chimpanzees, rhesus monkeys, lambs, cotton rats, mice, and guinea pigs. Although there isn't yet conclusive proof that RSV persists in humans, guinea pigs are a bit uncommon in that they can develop persistent or even latent infections. Additionally, there are a number of pneumoviruses that closely resemble human RSV, including bovine RSV (bRSV), ovine RSV, and the mouse pneumonia virus[227]. The homology between bRSV and hRSV over the whole genome is around 80%. Polyclonal antibodies that target hRSV typically detect bRSV proteins. The prevalence of the most severe sickness in young (6-month-old) people and the less severe disease in older animals are just a few of the characteristics that bRSV shares with hRSV. Since BRSV is a virus

for calves and as a result causes a condition that is almost equivalent to RSV in young human children, the bovine model has an advantage over mouse models in this regard. The bRSV model's pathological and clinical traits are reported.

Due to their simplicity in housing and handling, the availability of numerous transgenic and gene-deletion mice, as well as immunological reagents for defining immunopathological pathways, inbred laboratory mouse strains are the most often utilized models of hRSV infections[228]. The lung structure of mice is simpler than that of humans, and the more pronounced clinical symptoms of disease in mice, such as weight loss, lethargy, and ruffled fur, are non-specific. However, mice are at best semi-permissive hosts. Although some RSV strains may not cause AHR, acute RSV infection in mice can cause airway obstruction and AHR that can be detected by whole-body plethysmography. But even the most tolerant mouse strain, BALB/c, needs a very high intranasal inoculum to cause AHR (often 106 or 107 PFU). For comparison, mature people can become infected with as few as 1,000 PFU of an inoculum. Depending on the size of the inoculum, peak viral titers in the airways or lungs of mice are visible 4-5 days after inoculation, and the virus becomes undetectable by plaque assay by day 7 or 8 postinfection[229].

2.16 Genomic Predisposition to Serious RSV Infection

When stricter documentation requirements were used, the estimated heritable contribution to susceptibility for severe RSV sickness increased to 22%[230]. This emerged from an examination of concordance for RSV hospitalization in dizygotic and monozygotic Danish twin pairs. The discovery that the same RSV strain can cause symptoms ranging from mild upper respiratory symptoms to severe LRTI in the same season is another strong indicator of a genetic influence on illness severity. Gene polymorphisms, particularly those that result in altered expression or function of the gene

product, would support the involvement of the particular gene product in RSV-induced pathology[231]. Additionally, the different responses of different mouse strains to HRSV infection offer additional evidence of a genetic contribution in susceptibility to severe disease.

The risk of severe RSV disease was discovered to be primarily connected with the innate immune gene after 347 single nucleotide polymorphisms (SNPs) were evaluated in 437 Dutch infants who needed hospitalization due to RSV infection and 1008 controls**.[232]**. The five genes VDR (vitamin D receptor), JUN (encoding the Jun proto-oncogene, a transcriptional regulator), IFNA5 (encoding IFN-5), NOS2A (encoding inducible nitric oxide synthase), and FCERIA (encoding high-affinity IgE receptor-subunit) had the highest level of significance and associations at both the allele and genotype level. Later, it was shown that preterm children were overrepresented in the case sample and that 11 of the 347 SNPs under examination, nine of which were linked to genes encoding mediators of innate immunity, significantly affected the risk of premature birth[233]. Notably, six of these SNPs—IL27, C3, NFKBIA, and TGFBRI, which are protective, and IFNG and ADAM33, which increase risk—showed relationships with severe disease exclusively in premature children. ILIRN (encoding the IL-I receptor antagonist), however, increased the risk for term children while acting as a protective factor in the group with premature births. A variant of IFNAR2 was linked to protection in term infants but not in preterm infants, while a variant of IFNA13 raised the risk exclusively in term infants[234]. In the overall study cohort, the last gene had not demonstrated a meaningful connection. It should be noted that the odds ratios (ORs) found in these and other research typically range from 1.2 to 1.8 for risk alleles or genotypes and are infrequently lower than 0.7 for protective alleles or genotypes, indicating that each genetic relationship contributes very modestly to the overall risk. In black South African children, the relationship of severe

RSV disease with the Thrl Met SNP in the VDR gene, as seen in the Dutch multigene analysis, was confirmed, while the importance of particular genotype associations varied significantly in the two cohorts[235].

2.17 Prevention of RSV

Ideally, people with cold-like symptoms should not interact with children at high risk for severe RSV disease, including premature infants, children younger than 2 years of age with chronic lung or heart conditions, children with weakened immune systems, or children with neuromuscular disorders. If this is not possible, they should carefully follow the prevention steps mentioned above and wash their hands before interacting with such children. They should also refrain from kissing high-risk children while they have cold-like symptoms[236].

Parents of children at high risk for developing severe RSV disease should help their child, when possible, do the following

- Avoid close contact with sick people
- Wash their hands often with soap and water for at least 20 seconds
- Avoid touching their face with unwashed hands
- Limit the time they spend in childcare centers or other potentially contagious settings during periods of high RSV activity. This may help prevent infection and spread of the virus during the RSV season

The best primary preventative tactics continue to be washing hands after handling a patient or avoiding contact with those who are exhibiting respiratory symptoms. Depending on the situation, using alcohol-based hand rubs, antimicrobial soap, or soap and water to wash your hands is okay. Before being sent home after delivery, parents or other caregivers should receive counseling on these precautions[237]. Education should aggressively promote the health benefits of breastfeeding in the general prevention of infections and RSV disease as well as the avoidance of exposure to smoke from cigarettes. Both in congested homes and in the hospital setting, infection spreads swiftly. Because it frequently affects kids with currently

present morbidity, nosocomial RSV infection is linked to higher mortality than community-acquired disease [238].

2.18 Control Measures

Healthy adults and infants infected with RSV do not usually need to be hospitalized. But some people with RSV infection, especially older adults and infants younger than 6 months of age, may need to be hospitalized if they are having trouble breathing or are dehydrated. In the most severe cases, a person may require additional oxygen, or IV fluids (if they can't eat or drink enough), or intubation (have a breathing tube inserted through the mouth and down to the airway) with mechanical ventilation (a machine to help a person breathe). In most of these cases, hospitalization only lasts a few days. Routine RSV entrance screening, increased sanitation of the hands, and cohort nursing with personal protective equipment (PPE) eye protection, nose and face masks, laboratory coats and gloves) are all examples of control measures[239].

2.19 Immunization

It would be ideal to prevent the significant load of RSV that occurs in the first year of life through maternal vaccination or vaccination of the infant. Unfortunately, none of the potential infant vaccines are close to commercialization[240]. Due to safety issues that surfaced during clinical trials of a formalin-inactivated Fl-RSV vaccine in the 1960s, researchers were reluctant to investigate inactivated vaccines, which contributed to the difficulties in developing an infant RSV vaccination. Two infants died as a result of that vaccine, which caused recipients to develop more serious RSV sickness. Two live attenuated vaccines that have recently showed some promises are being evaluated, while subunit vaccinations are currently being tested on adults**.** The reader is directed to thorough summaries of the difficulties in developing an RSV vaccine[241].

Infant RSV hospitalization can be prevented with passive immunization; however, this method is not widely available due to its high cost and rigorous monthly intravenous dosing schedule. A genetically modified humanized monoclonal antibody called palivizumab has been available in Canada since 1999, and it is routinely administered to some high-risk newborns in all provinces. In a multicenter RCT [242], the product's efficacy and safety were demonstrated. Over the course of the RSV season, infants received five monthly injections of palivizumab (15 mg/kg) or a placebo. Palivizumab was used in a comparable, large-scale RCT in patients with hemodynamically severe heart disease that also showed reductions in RSV hospitalization. Following the regulatory approval of palivizumab prophylaxis in North America as a result of these critical trials, regular prophylaxis for high-risk children was subsequently advised globally [243]. All newborns less than 36 weeks GA who live in remote northern rural communities without access to medical care, as well as full-term Inuit infants, are also advised to receive prophylaxis, according to the Canadian Paediatric Society[244].

2.20. Brief History of Respiratory Viruses of Importance to This Study

RSV was discovered in 1956 when researchers isolated a virus from a population of chimpanzees with respiratory disease. They gave the virus the name Chimpanzee Coryza Agent (CCA). In 1957, the same virus was identified by Robert M. Chanock in children with respiratory disease. Human antibody studies in infants and children showed that the infection occurred in the early stages Life was common. The virus was later renamed Human Orthopneumovirus or Human Respiratory Syncytial Virus (hRSV). Several other pneumoviruses bear close similarity to hRSV. BovineRSV (bRSV) shares approximately 80% of its genome with hRSV. It also shares hRSV's predilection for young animals, causing more severe disease in calves younger than six months. Because bRSV-infected calves have

almost identical symptoms to hRSV-infected children, they have proven to be an important animal model in RSV research[245].

The influenza A virus (IAV) is an age-long pathogen that causes influenza in birds and some mammals, including humans. It is an RNA virus whose subtypes were isolated from wild birds. Occasionally, it is transmitted from wild birds to domestic birds, which can result in serious illness, outbreaks, or influenza pandemics in humans. Each virus subtype has mutated into a variety of strains with different disease profiles; Some can cause disease in only one species, others in several[245].

The influenza B virus is the only species of the genus Betainefluenzavirus in the virus family Orthomyxoviridae. The influenza B virus is known to only infect humans, pigs and seals. This limited host range appears to be responsible for the lack of associated influenza pandemics, in contrast to those caused by the morphologically similar influenza A virus, as both mutate by both antigenic drift and assortment. There are two known circulating lineages of influenza B virus based on the antigenic properties of the surface glycoprotein hemagglutinin. The lineages are referred to as B/Yamagata/16/88-like and B/Victoria/2/87-like viruses. The CDC-licensed quadrivalent influenza vaccine is currently designed to protect against both co-circulating lineages and has been shown to be more effective in preventing influenza caused by the influenza B virus than the current trivalent vaccine. To further mitigate the effects of this virus, influenza B viruses evolve slower than A viruses and faster than C viruses in humans. Influenza virus B mutates two to three times slower than type A. Nevertheless, it is believed that the influenza B virus could cause significant morbidity and mortality worldwide and have a significant impact on adolescents and school children.

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by the SARS-CoV-2 virus. The first known case was identified in Wuhan, China, in December 2019. The disease quickly spread worldwide, leading to the COVID-19 pandemic. Symptoms of COVID-19 vary but often include fever, cough, headache, fatigue, difficulty breathing, loss of smell and loss of taste. Symptoms can appear one to fourteen days after exposure to the virus. At least a third of those infected do not develop any noticeable symptoms. Of those who develop symptoms significant enough to be classified as patients, most (81%) develop mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia or more than 50% lung involvement on imaging) and 5% develop critical symptoms (respiratory failure, shock, or multiorgan dysfunction). Older people are at higher risk of developing severe symptoms. Some people experience a range of effects (long COVID) years after infection and organ damage has been observed. Multi-year studies are underway to further investigate the long-term effects of the disease. COVID19 is transmitted when infectious particles are inhaled or come into contact with the eyes, nose, or mouth. The risk is highest when people are in close proximity. However, small airborne particles containing the virus can become suspended in the air and spread over longer distances, especially indoors. Transmission can also occur when people touch their eyes, nose or mouth after touching surfaces or objects contaminated with the virus. People remain contagious for up to 20 days and can spread the virus even if they don't develop symptoms.

2.21. Immune Response in Respiratory Infections

The respiratory system is constantly exposed to the external environment and therefore must be prepared to respond to and eliminate pathogens. Viral clearance and resolution of infection requires a complex, multifaceted response initiated by resident respiratory tract cells and innate immune cells and ultimately resolved by adaptive immune cells. Although an effective

immune response is essential to eliminate viral pathogens, a prolonged or exaggerated response can damage the respiratory system. Immune-mediated lung injury manifests clinically in different ways depending on the location and extent of the injury. Thus, the antiviral immune response represents a balancing act between elimination of the virus and immune-mediated lung injury[246].

Almost all cells in the body have mechanisms to recognize viruses (and other microbial pathogens) through pattern recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs), or molecules that are associated with viral and microbial pathogens but are not normally present in host cells. PRRs important for virus detection include Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I), NOD-like receptors (NLRs), and other cytosolic virus sensors. Although these receptors are expressed in many cell types, their activation in respiratory epithelial cells, which are typically among the first cell types to become infected, is critical for limiting virus spread and alerting the immune system to respond to the infection. Activation of PRRs in these cells by viral infection triggers the production and release of type I and III interferons (IFNs) and other proinflammatory mediators (e.g., cytokines, chemokines, and antimicrobial peptides) that stimulate the host's innate and adaptive immune response trigger[246]. Thus, the degree of PRR activation throughout the respiratory tract ultimately influences the degree of immune cell recruitment and release of proinflammatory mediators and subsequently any resulting immunopathology[246].

2.22.1 Interferon Response

Type I IFNs (IFN- and IFN-) many different types of cellular sensors can detect viruses and induce the expression of type I IFNsIFN- and IFN-. Type I IFNs bind to the ubiquitously expressed IFNAR (IFN/receptor) and thus activate the JAK/STAT signaling pathway. Viral

entry receptor Common symptoms Clinical complicationsRhinovirus ICAM-1 or LDL Rhinorrhea, runny nose, sneezing, sore throat, cough respiratory disease, bronchitis. Common coronavirus. Strain-specific fever, rhinorrhea, runny nose, sneezing, sore throat, cough. Mild to moderate upper respiratory tract disease. Adenovirus strain-specific penton. Fever, rhinorrhea, runny nose, sneezing, sore throat, cough, pink eye, diarrhea, bladder infections Mild to moderate upper respiratory illness, croup, tonsillitis. Seasonal flu. Sialic acids. Fever, rhinorrhea or nasal congestion, runny nose, sore throat, cough, headache, myalgia. Mild to moderate upper respiratory tract disease, bronchitis, croup. RSV nucleolin fever, rhinorrhea, runny nose, sore throat, cough, wheezing, shortness of breath. Mild to moderate upper respiratory tract disease, bronchitis, bronchiolitis, croup. Enterovirus D68, sialic acids alpha2-6, rhinorrhea, sneezing, cough, mouth blisters, myalgia; Wheezing and dyspnea in more severe cases. Mild to moderate upper respiratory tract disease, bronchitis, bronchiolitis, pneumonia. Influenza pandemic Alveolar damage, acute respiratory distress syndrome, respiratory failure.

SARS-CoV ACE2 fever, chills, cough, shortness of breath, dyspnea, myalgiaRapidly progressive pneumonia, diffuse alveolar damage, severe acute respiratory distress syndrome, respiratory failure, fibrosis.

MERS-CoV CD26 fever, chills, runny nose, sore throat, nonproductive cough, sputum production, shortness of breath, dyspnea, headache, vomiting, diarrhea, myalgia. Rapidly progressive pneumonia, diffuse alveolar damage, severe acute respiratory distress syndrome, respiratory failure, septic shock and multi-organ failure

2.22.2 Epithelial Cell

Cytokines, chemokines, and other factors discussed in this section are also secreted by many types of immune cells (discussed later) and therefore cause similar pathological or protective

effects. Cytokines Airway epithelial cells secrete a variety of cytokines, chemokines, antimicrobial peptides, and other factors in response to viral infection. Cytokines beyond the IFNs produced by the airway epithelium include interleukin-6 (IL-6), tumor necrosis factor (TNF-), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage-CSF (GMCSF). IL-6 and TNF- are potent proinflammatory cytokines that modulate many types of immune cells. IL-6 facilitates the transition from innate to adaptive immune response by reducing neutrophil activity while promoting monocyte and T cell recruitment, differentiation and activity. High IL-6 levels correlate with disease severity, but attenuation of IL-6 signaling can lead to uncontrolled viral replication and therefore higher mortality. TNF impairs viral replication, increases cytotoxic activity and cytokine production by leukocytes, and activates endothelial cells[245].

Elevated TNF levels have been associated with higher morbidity during infection with highly pathogenic viruses, and the blocking activity of TNF- attenuates immune-mediated pathology. G-CSF and GM-CSF both induce the differentiation of myeloid lineage cells. G-CSF stimulates the production, differentiation, proliferation and survival of neutrophils, thereby mobilizing one of the first responder neutrophils. GM-CSF stimulates the proliferation and differentiation of various types of immune progenitor cells. In the lung, GM-CSF induces the expansion and activation of pulmonary DCs and macrophage immune responses, which are required for an effective T cell response and viral clearance. Mice lacking GMCSF signaling are highly susceptible to respiratory viral infections, and exogenous delivery of GM-CSF is protective[246].

2.22.3 Chemokines

Chemokines produced by the airway epithelium stimulate the migration of both innate and adaptive immune cells to the lung. IL-8/CXCL8 recruits neutrophils to the lung, stimulates

degranulation and subsequent release of cytotoxic and inflammatory mediators, and may support neutrophil survival. Elevated IL-8 levels are associated with the pathogenesis of acute respiratory distress syndrome (ARDS) as tissue damage is likely caused by excessive release of neutrophil proteases and reactive oxygen species (ROS). IP-10/CXCL10 stimulates chemotaxis of T cells, NK cells and monocytes and additionally promotes monocyte and DC activation along with other cytokines. CXCL10/IP-10 may be protective in some cases as neutralization of IP-10 worsens disease caused by respiratory viral infection. In other cases, CXCL10/IP-10 may contribute to extensive leukocyte recruitment, leading to an increased inflammatory response and immune-mediated lung injury[246].

2.24. RSV and its Proteins

In vitro, 95% of the virus's offspring remains attached to the cell surface as particles that appear to be incomplete in budding. In the process of generating virus stocks, infected cells are often exposed to freeze-thawing, sonication, or vortexing to release attached virus. Ninety-five percent of the virus progeny in vitro stay affixed to the cell surface as particles that don't seem to be fully budding. Infected cells are frequently subjected to freeze-thawing, sonication, or vortexing in order to release associated virus during the process of creating virus stocks. RSV is a moderately sized (~150 nm) enveloped virus. There are certain filamentous strains of particles, despite the majority being spherical[239,240] .The envelope including viral glycoproteins and a matrix protein encases the helical nucleocapsid holding the DNA. The RSV virion's components include a nucl, however doing so increases cellular contamination and decreases infectivity[244]. Particle instability and aggregation lead RSV to lose infectivity rapidly during handling and freeze-thawing; however, excipients such as sucrose can help mitigate this problem[246]. There is indirect evidence that the glycoproteins on the surface, especially F, are involved in instability[247, 248]. The particle's long filamentous

form is also thought to make it fragile. The RSV envelope comprises three viral transmembrane surface glycoproteins: the large glycoprotein G, the fusion protein F, and the small hydrophobic SH protein. The non-glycosylated matrix M protein is present on the envelope's inner surface. The viral glycoproteins exist as separate homo-oligomers, which appear as short (11-16 nm) surface spikes. RSV lacks neuraminidase or hemagglutinin activity, and F is heavily sialylated, likely because of the lack of a neuraminidase. There are four nucleocapsid/polymerase proteins: the nucleoprotein N, the phosphoprotein P, the transcription processivity factor M2-1, and the large polymerase subunit L (Fig. 5).

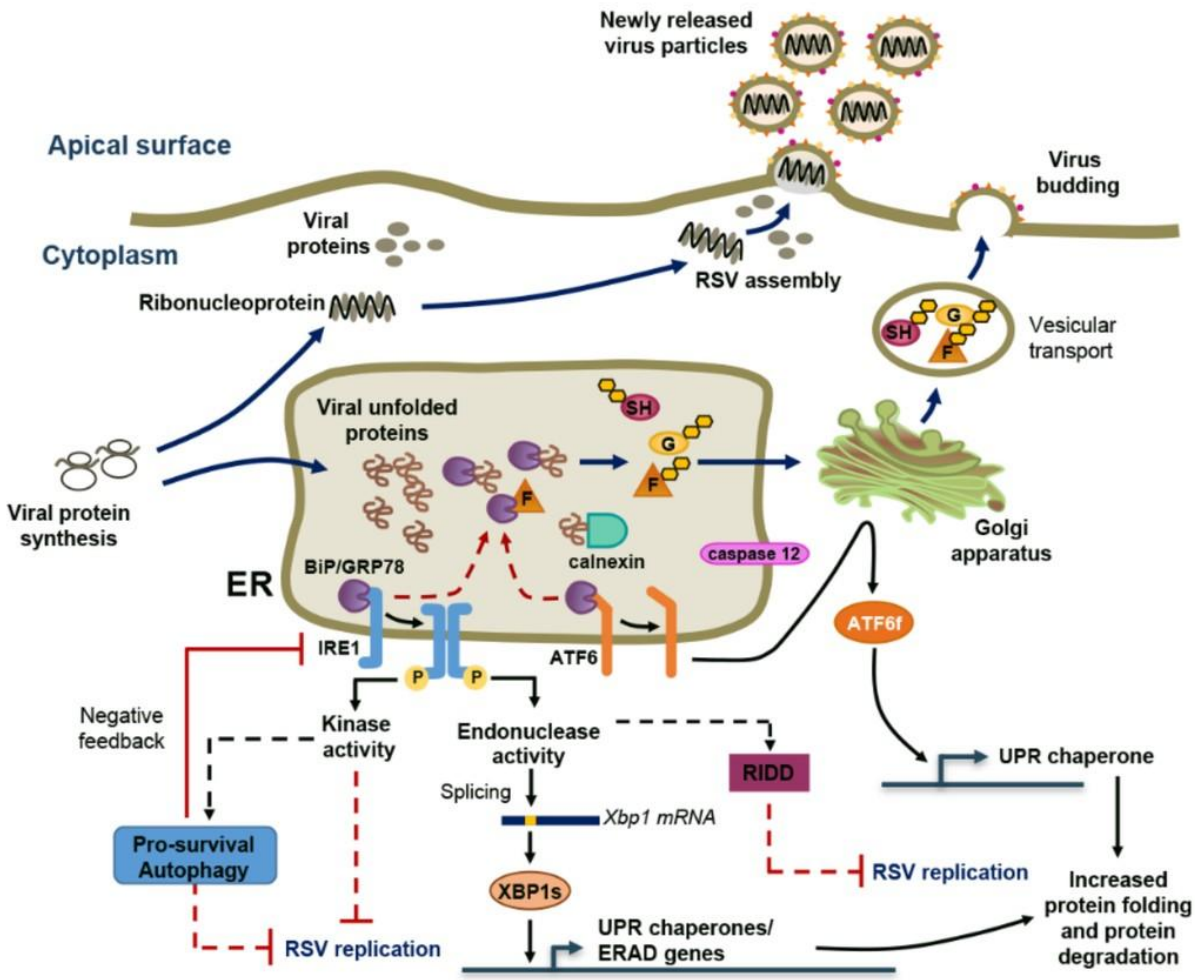


Figure: 2.5

Source[247]

This binding has the potential to modify cellular chemotaxis and decrease immune cell migration into infected people' lungs[249]. Moreover, G protein modifies the host immune response by obstructing the signaling of many toll-like receptors, such as TLR4241[249]. Surface protein F (fusion protein) is responsible for fusion of viral and host cell membranes, as well as syncytium formation between viral particles[22]. Its sequence is highly conserved between strains[242]. While viral attachment appears to involve both F and G proteins, F fusion occurs independently of G[249] F protein exists in multiple conformational forms[239,241]. In the prefusion state (PreF), the protein exists in a trimeric form and contains the major antigenic site Ø[239]. Ø serves as a primary target of neutralizing antibodies in the body[241]. Following attachment to its target on the surface of the host cell (although the specific binding agent remains unclear), PreF undergoes a structural alteration resulting in the loss of Ø[239, 241]. This transformation allows the protein to integrate itself into the host cell membrane, leading to the merging of the viral and host cell membranes[239]. A final change in structure yields a more stable and elongated form of the protein (PostF, or post-fusion)[241]. In contrast to the RSV G protein, the RSV F protein activates toll-like receptor 4 (TLR4), initiating both the innate immune response and signal transduction[239, 249]. The total number of proteins identified in RSV, including the two surface glycoproteins, is 11, and these proteins are further delineated in the table below.

2.25. RSV Replication Cycle

2.25.1. Entry of RSV and its Host Binding Receptors

RSV virion entrance into host cells is primarily initiated by the fusion of the virus and host cell membranes, as well as the coupling of virions with host cell surface components. Three structural proteins-SH, G, and F-are encoded to locate on the surface of the virus, as was mentioned earlier. The RSV SH protein is not necessary for in vitro infection. Consequently,

the next sections focus on important developments in understanding the interaction between RSV G and F proteins and a host cell. The primary function of the viral G protein is to interact with host cell adhesion molecules to attach virions to the cell surface[250]. Peripheral membrane protein Annexin II is expressed on endothelial cells in different tissues and organs and performs a variety of functions on the cell surface. For example, in a calcium-dependent way, annexin II has a significant affinity for phospholipids on the surface of endothelial cells treated with EGTA. Annexin II seems to increase the cancer cells' adherence to hepatic sinusoid endothelial cells on metastatic lymphoma cells[229]. Moreover, tenascin C, an extracellular matrix component, binds robustly to annexin II on gliomas and endothelial cells, provoking migration, cell proliferation, and focal adhesion loss[243]. Annexin II has also been identified as a prospective RSV receptor, binding to the RSV G protein in Hep2 cells, an interaction that can be obstructed by the selectin antagonist TBC1269[251]. The occurrence of RSV infection in immortalized cell lines may be facilitated by the presence of Heparan sulfate proteoglycan (HSPG) and other glycosaminoglycans (GAGs) on the host cell surface, which can promote the binding of positively charged residues found in the heparin-binding domain (HBD) of the RSV G protein. A study also shows, in Hep-2 cells that were infected, the G protein expressed by an RSV virion had a molecular weight of 95 kDa after glycosylation, while its polypeptide skeleton had a molecular weight of 32 kDa[252]. On the other hand, in HBE culture, which had both laboratory-adapted strains and clinical isolates of RSV subgroups A and B, a G protein with higher levels of glycosylation and a greater molecular weight of 170 kDa was produced, as reported by a study[253]. Nonexistence of Heparan sulfate proteoglycans (HSPG) on the surface of human ciliated airway epithelial cells resulted in a substantial reduction in the communication between G and HSPG in such cells[254]. In contrast, in human airway epithelial (HAE) culture, CX3C chemokine receptor 1 (CX3CR1) located on the top surface of ciliated cells binds with CX3CL1, causing adhesion

and movement. A study has confirmed the association between host CX3CR1 and RSV G. In culture, a non-neutralizing monoclonal antibody (mAb) against the CX3C motif of the viral G protein could prevent RSV from effectively infecting. Moreover, CX3CR1-deficient mice were significantly less vulnerable to RSV infection than CX3CR1-expressing mice[255].

The surface of RSV contains a significant glycoprotein known as the F protein, which is categorized as a class I fusion protein. This protein is a trimer that is anchored to the RSV membrane via a transmembrane domain and is under a high level of tension. The binding receptors of the F protein have been extensively researched and analyzed. Toll-like receptor 4, which is a member of the Toll-like receptor family and a pattern recognition receptor, is a receptor known to be sensitive to lipopolysaccharide (LPS) from gram-negative bacteria. It has been demonstrated that TLR4 can trigger the activation of the innate immune system, including the intracellular NF-κB signaling pathway and inflammatory cytokines[256]. The persistence of RSV replication was found to be longer in TLR4-deficient mice compared to normal mice, indicating that the expression of TLR4 plays a crucial role in regulating RSV replication in vivo and also modulates the innate immune response of monocytes to generate IL-6 in response to exposure to RSV F protein Intercellular adhesion molecule-1 (ICAM-1), a type 1 glycoprotein in the immunoglobulin superfamily that binds to the RSV F protein and is required for viral infection and reproduction, facilitates RSV infection and entry into human epithelial cells[257,258]. Furthermore, a study found that fusion of host-virus membranes might result by interaction between the RSV F protein and the epidermal growth factor receptor (EGFR), which is located on the apical surface of bronchial epithelial cells[259]. Another study[260], discovered that in vitro, the F protein of RSV interacted with nucleolin (NCL) of host cells and selectively attached to NCL present on the apical cells' surface. The authors utilized confocal microscopy to demonstrate that RSV virions and NCL were colocalized at the surface of the cultured cells. The researchers observed a significant reduction in the

colocalization of RSV and NCL proteins on the cell surface when NCL-specific antibodies were preincubated with the cells[260]. In a separate study, it was found that NCL and TLR4 levels that were colocalized with the F protein increased in the early stages of infection and then decreased. Despite being the most extensively examined receptor among those mentioned previously, NCL has been demonstrated to engage with numerous other viruses, such as HIV-1, human parainfluenza virus type 3, enterovirus 71, human influenza A, and rabbit hemorrhagic disease virus[261-265]. These results indicate that NCL might function as a co-factor of the RSV F protein rather than serving as a principal binding receptor. Recently, Griffiths et al. identified insulin-like growth factor 1 receptor (IGF1R) as a novel RSV receptor, which could provide new insights into RSV entry into the host[266].

The RSV G protein begins to enter the cell through the process of endocytosis. RSV G protein is required for the activation of ATP1A1, a Na+/K+ transport subunit alpha 1. This process is triggered by RSV infection. Consequently, EGFR is transactivated by c-Src tyrosine kinase through phosphorylation at Tyr845[267]. The signals that follow EGFR cause actin to reorganize, causing the plasma membrane to wrinkle and allowing fluids and RSV to be absorbed by means of macropinosomes that protrude from the membrane. The viral envelope carrying RSV enters the large, liquid-filled macropinosomes, promoting fusion between RSV and host membranes and ultimately allowing RSV to enter the host cell. San-Juan-Vergara et al. suggested that the penetration of RSV into primary NHEB cells is instigated by RSV binding to plasma membrane constituents that are rich in cholesterol, promoting the semifusion of the RSV envelope and the plasma membrane. Complete fusion occurs during endocytosis in the endosome[268]. Krzyzaniak et al. contend that the entry of RSV particles is governed by the interaction of the RSV F protein with EGFR, leading to the activation of the signal cascade of PI3K, PAK1, and downstream effectors in the host cells. They argue that this sequence of signals results in a succession of disruptions, including actin

reorganization, the formation of vesicles in the plasma membrane, and a notable rise in fluid absorption, which prompts macrophage-driven internalization. In macropinosomes where Rab5 is functional, the RSV F protein is cleaved for the second time through the activity of a furin-like enzyme that does not require acid, eventually penetrating the host[269]. Recently, a study proposed that the bond between the RSV F glycoprotein and IGF1R activates protein kinase Cζ (PKC zeta), which in turn facilitates the movement of NCL from the nucleus to the plasma membrane, thereby boosting the adhesion and penetration of RSV virions into host cells [239, 266]. The corresponding experiments demonstrated that inhibiting PKCζ lowered RSV infection to the same degree as blocking the interaction between RSV and NCL.

2.25.2. Pathogenesis of RSV

Collins and Graham [270] state that RSV can spread through the air, by contact with an infected person's mouth, nose, or eyes, or by touching contaminated objects. According to another study, RSV may live for a long time on a variety of surfaces, including skin, gloves, furniture, and textiles[260]. This suggests that RSV is extremely contagious. Pneumonia or bronchiolitis, an inflammation of the bronchioles inside the tiny airways, can result after an RSV infection. Pneumonia caused by RSV in children can cause respiratory symptoms as fever, chills, nausea, wheezing, chest pain, and other respiratory problems[271,272].

Similarly, bronchiolitis caused by RSV is characterized by coughing, fever, wheezing, dyspnea, tachypnea, and fatigue[273]. As these illnesses can be life-threatening, infants with severe RSV symptoms require hospitalization to receive essential medical treatment.

Once RSV enters the oral or nasal cavities, it immediately invades the upper respiratory tract airway epithelial cells (AECs), before moving on to the lower respiratory system and penetrating the bronchioles, where viral replication is more efficient, as evidenced by studies in mice and newborn respiratory tissues[274-276]. The primary cells that RSV targets are the

ciliated cells in the bronchial epithelium and the type 1 pneumocytes in the alveolus[277]. Additionally, using in vitro cultures, RSV has demonstrated its ability to infect intraepithelial dendritic cells (DCs) and basal epithelial cells of the conductive airways[278]. As a result, RSV has a diverse range of cellular reservoirs within the human host's respiratory tract that aid in its pathogenesis, leading to symptoms such as fever, fatigue, and rapid breathing. Research using an in vitro AEC model has shown that RSV infection is confined to small clusters of ciliated apical cells or non-contiguous groups of cells within the epithelium of large airways[279]. As the infection worsens, RSV leads to the loss of ciliation, occasional development of syncytium, and hypersecretion of mucus. These effects can result in the formation of thick plugs in the bronchiolar lumen in vivo[280]. Additionally, RSV has the ability to separate apical AECs in living organisms, which exposes nociceptive nerve fibers and triggers a cough response[281].

Well-differentiated primary pediatric bronchial epithelial cells (WD-PBEC) offer a good in vitro representation for investigating RSV infection. Because WD-PBECs have intact tight connections and a polarized pseudostratified multilayered epithelium made up of ciliated, goblet, and basal cells, it is possible to replicate the morphological, physiological, and functional characteristics of the respiratory tract in an in vitro model[280,281]. Unlike post-mortem lung samples obtained from RSV-infected individuals, RSV infection in the WD-PBEC in vitro model does not result in extensive airway epithelial damage[282]. Subsequent investigations conducted in vitro revealed that despite the majority of ciliated cells being infected with RSV, the monolayer of cells remains intact. Other studies corroborate these findings and indicate that the highest level of RSV infection in ciliated cells is observed on the fourth day following infection (p.i.) and substantially diminishes by the eighth day p.i.[282]. This suggests that immune-cell-mediated mechanisms are not necessary to clear RSV-infected ciliated cells from the epithelium between days four and eight p.i. In addition, WD-

PBEC cells exhibited ciliated cell detachment and death, consistent with histopathological investigations of infants with fatal RSV, where bronchiolar epithelial cells exhibited caspase-3 activity[279]. According to a study, an in vitro study revealed that ciliated cells infected with RSV die when they detach from the epithelium[282]. Sick individuals, especially hospitalized newborns, experience blockages in the lower airways due to RSV-infected AECs that have shed from the airway epithelium[274, 275]. In a study, RSV NS2 was identified as the viral protein responsible for promoting the rounding and sloughing of infected ciliated cells, as demonstrated through the use of RSV gene deletion mutants and gain-of-function experiments involving recombinant PIV3-NS2 expressing RSV NS2[282]. Furthermore, using an in vivo model, a study demonstrated that excessive mucus production is a characteristic of RSV pathogenesis[239]. Although RSV does not infect goblet cells or stimulate them to secrete mucus, it does impact the basal cells of the airway epithelium, which differentiate into mucus-secreting cells according to an in vitro culture model[282]. The discovery of goblet cell hyperplasia in the lungs of patients with fatal RSV infections suggests that RSV indirectly triggers mucus production in the bronchial lumen by promoting goblet cell proliferation[279]. As a result, RSV infection of the respiratory tract leads to the formation of mucus plugs and detachable ciliated AECs, as well as a significant reduction in mucociliary transport (MCT), which normally expels mucus plugs from the airways in less than five days. Therefore, the accumulation of these plugs in the bronchial lumen is responsible for the viral agent's pathogenesis[283]. Consequently, RSV infection causes necrosis of the airway epithelium, edema of the submucosa, and blockage of the bronchial lumen[276, 277,284].

Recently, it has been demonstrated that the production of Interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP), two crucial cytokines for the onset of allergic asthma, is induced by RSV infection[285, 286,287]. Both in vivo and in vitro models have shown that the production of these cytokines has a significant impact on RSV pathogenesis. As detailed in

the subsequent section, TSLP and IL-33 release lead to an inflammatory environment that results in increased mucus secretion, eosinophil and neutrophil counts, and higher levels of T helper (Th) 2 cytokines such as IL-5 and IL-13[288] in the lungs of RSV-infected individuals. Simultaneously, there is a decrease in the total number of CD4+ and CD8+ T lymphocytes in those with RSV infection[289, 290]. Recent studies have revealed that RSV infection triggers the production of two cytokines, interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP), which play crucial roles in the development of allergic asthma[291, 292,293,294]. Using in vivo and in vitro models, it was demonstrated that the generation of these cytokines significantly influences RSV pathogenesis. In fact, the release of TSLP and IL-33 creates an inflammatory environment that enhances mucus production, eosinophil and neutrophil counts, and levels of the Th2 cytokines IL-5 and IL-13[288] in the lungs during RSV infection. This matter will be discussed in more detail in the following section. Additionally, RSV infection is accompanied by a simultaneous decline in the overall number of CD4+ and CD8+ T cells[290, 295].

Endnotes

1. E. Kamau, J. R. Otieno, C. S. Lewa, A. Mwema, N. Murunga, D. J. Nokes & C. N, Agoti. *Evolution of Respiratory Syncytial Virus Genotype BA in Kilifi, Kenya 15 years, on,* **Scientific Reports,** 10(1), 2020, 1-12.

2. *A., Mejias, R., Rodríguez-Fernández, S., Oliva, M. E., Peeples, & O. Ramilo, The Journey to A Respiratory Syncytial Virus Vaccine*, **Annals of Allergy, Asthma & Immunology,** 125(1), 2020, 36-46.

3. Y. A. Mebratu, & Y. Tesfaigzi. Is IL-1β a Target for Reducing Hospitalization of Infants Infected with Respiratory Syncytial Virus, **American Journal of Respiratory Cell and Molecular Biology,** 66(3), 2022, 248-249.

4. J. N. Harding, D. Siefker, L. Vu, D. You, J. De. Vincenzo, J. F. Pierre & S. A. Cormier, Altered gut Microbiota in Infants is associated with Respiratory Syncytial Virus Disease Severity, **BMC Microbiology,** 20(1), 2020, 1-11.

5. H. H. Nam, & M. G. Ison, *Respiratory Syncytial Virus Infection in Adults*, ***BMJ*, 366** 2019. K. Bohmwald, N. M. Gálvez, G. Canedo-Marroquín, M. S. Pizarro-Ortega, C. Andrade-Parra, F. Gómez-Santander & A. M. Kalergis, *Contribution of Cytokines to Tissue Damage during Human Respiratory Syncytial Virus Infection*, **Frontiers in Immunology,** 10, 2019, 452.

6. P. Sitthicharoenchai, S. Alnajjar, & M. R. Ackermann, A model of Respiratory Syncytial Virus (RSV) Infection of Infants in Newborn Lambs, **Cell and Tissue Research,** *380*, 2020 313-324. H. M. Li, R. Ghildyal, M. Hu, K. C. Tran, L. M. Starrs, J. Mills & D. A. Jans, *Respiratory Syncytial Virus Matrix Protein-Chromatin Association is key to Transcriptional Inhibition in Infected Cells*, ***Cells*,** 10(10), 2021, 2786.

7. J. Fernandez-Sarmiento, S. C. Corrales, E. Obando, J. Amin, A. B. Goyes, P. A. B Lopez & N. B. Ortiz, *Factors associated with Severe Acute Respiratory Infections due to Rhinovirus/Enterovirus Complex in Children and their Comparison with those of Respiratory Syncytial Virus*, **Archives of Pediatric Infectious Diseases,** 10(2), 2022.

8. S. Melebari, *Etiology of Respiratory Infections among Neonatal and Pediatric Inpatients in a Tertiary Hospital in Makkah*, Saudi Arabia, **EC Pediatrics,** 2022 *11*, 24-32. Z. Zheng, J. L. Warren, E. D. Shapiro, V. E. Pitzer, & D. M. Weinberger, *Estimated Incidence of Respiratory Hospitalizations Attributable to RSV Infections Across Age and Socioeconomic Groups*, **Pneumonia,** 14(1), 2022, 6.

9. K. Alshaghdali, M. Saeed, M. A. Kamal, & A. Saeed, *Interaction of Ectodomain of Respiratory Syncytial Virus G Protein with TLR2/TLR6 Heterodimer: An in Vitro and in Silico Approach to Decipher The Role of RSV G Protein in Pro-Inflammatory Response Against the Virus*, **Current Pharmaceutical Design,** 27(44), 2021, 4464-4476.

10. J. M. Su, M. Z. Wilson, C. E. Samuel & D. Ma, *Formation and Function of Liquid-Like Viral Factories in Negative-Sense Single-Stranded RNA Virus Infections*, **Viruses,** 13(1), 2021, 126.

11. E. J. Choi, W. Wu, X. Cong, K. Zhang, J. Luo, S. Ye, & X. Bao, *Broad Impact of Exchange Protein Directly Activated by cAMP 2 (EPAC2) on Respiratory Viral Infections*, **Viruses,** 13(6), 2021, 1179.

12. S. Ahmed, M. K. Khudair & T. Ahmed, *Study Role of Respiratory Syncytial Virus Associated with Infection of Respiratory System of Children in AL-Miqdadiya/Diyala*, **Indian Journal of Forensic Medicine & Toxicology,** 15(3), 2021, 5519.

13. L. Mohebi, H. Karami, N. Mirsalehi, N. H. Ardestani, J. Yavarian, M. Mard-Soltani & V. Salimi, *A Delayed Resurgence of Respiratory Syncytial Virus (RSV) during the COVID-19 Pandemic: An Unpredictable Outbreak in a Small Proportion of Children in the Southwest of Iran*, April **Journal of Medical Virology,** 94(12), 2022, 5802-5807.

14. J. H. Kim, H. Y. Kim, M. Lee, J. G. Ahn, J. Y. Baek, M. Y. Kim & J. M. Kang, *Respiratory Syncytial Virus Outbreak without Influenza in the Second Year of the Coronavirus Disease 2019 Pandemic: A National Sentinel Surveillance in Korea, 2021-2022 Season*, **J. Korean Med. Sci,** 37, 2022 258.

15. B. Hughes, D. Duong, B. J. White, K. R. Wigginton, E. M. Chan, M. K. Wolfe & A. B. Boehm, *Respiratory Syncytial Virus (RSV) RNA in Wastewater Settled Solids Reflects RSV Clinical Positivity Rates*, **Environmental Science & Technology Letters,** 9(2), 2022, 173-178.

16. A. B. Boehm, B. Hughes, D. Duong, V. Chan-Herur, A. Buchman, M. K. Wolfe, & B. J. White, *Wastewater Surveillance of Human Influenza, Metapneumovirus, Parainfluenza, Respiratory Syncytial Virus (RSV), Rhinovirus, and Seasonal Coronaviruses during the COVID-19 Pandemic*, **medRxiv**, 09, 2022, 20-22.

17. B. Schmoele-Thoma, A. M. Zareba, Q. Jiang, M. S. Maddur, R., Danaf, A. Mann, & K. A. Swanson, *Vaccine Efficacy in Adults in A Respiratory Syncytial Virus Challenge Study*, ***New England Journal of*** **Medicine,** 386(25), 2022, 2377-2386.

18. C. Munkstrup, F. K. Lomholt, H. D. Emborg, K. L. Møller, J. S. Krog, R. Trebbien, & L. S. Vestergaard, *Early and Intense Epidemic of Respiratory Syncytial Virus (RSV) in Denmark, August to December 2022*, **Eurosurveillance,** 28(1), 2023, 2200937.

19. A. Rajan, A. M. Weaver, G. M. Aloisio, J. Jelinski, H. L. Johnson, S. F. Venable & P. A. Piedra, *The Human Nose Organoid Respiratory Virus Model: An Ex Vivo Human Challenge Model to Study Respiratory Syncytial Virus (RSV) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pathogenesis and Evaluate Therapeutics*, **Mbio,** 13(17), 2022, 03511-21.

20. M. Meyer, E. Ruebsteck, F. Eifinger, F. Klein, A. Oberthuer, S. van Koningsbruggen-Rietschel & L. T. Weber, *Morbidity of Respiratory Syncytial Virus (RSV) Infections: RSV Compared With Severe Acute Respiratory Syndrome Coronavirus 2 Infections in Children Aged 0–4 Years in Cologne, Germany*, **The Journal of Infectious Diseases,** *226*(12), 2022, 2050-2053.

21. P. Sutto-Ortiz, S. Tcherniuk, N. Ysebaert, P. Abeywickrema, M. Noël, A. Decombe & E. Decroly, *The Methyltransferase Domain of the Respiratory Syncytial Virus L Protein Catalyzes Cap N7 and 2'-O-Methylation,* **PLoS Pathogens,** 17(5), 2021, 1009562.

22. O. Dolnik, G. K. Gerresheim & N. Biedenkopf, *New Perspectives on The Biogenesis of Viral Inclusion Bodies in Negative-Sense RNA Virus Infections*, ***Cells*,** 10(6), 2021, 1460.

23. A. Letafati, F. S. Aghamirmohammadali, A. Rahimi-Foroushani, S. A. Hasani, T. Mokhtari-Azad & J. Yavarian, *No Human Respiratory Syncytial Virus but SARS-CoV-2 found in Children Under 5 Years Old referred to Children Medical Center in 2021, Tehran, Iran*, **Journal of Medical Virology,** 94(7), 2022, 3096-3100.

24. T. Corsello, Y. Qu, T. Ivanciuc, R. P. Garofalo & A. Casola, *Antiviral Activity of Extracellular Vesicles derived from Respiratory Syncytial Virus-Infected Airway Epithelial Cells*, **Frontiers in immunology,** 13, 2022, 1.

25. K. Huang, T. Ying & Y. Wu, *Single-Domain Antibodies as Therapeutics for Respiratory RNA Virus Infections*, **Viruses,** 14(6), 2022, 1162.

26. A. Schadenhofer, *Respiratory Syncytial Virus Reverse Genetics for Identification of Molecular Determinants of Strain Specific Phenotypic Changes,* ***Doctoral Dissertation****, Dissertation, Hannover, Tierärztliche Hochschule Hannover,*11, 2021, 22.

27. P. Mittal, R. Kapoor, A. Saharan & R. K. Gautam, *Targeting Molecular and Cellular Mechanisms in Respiratory Syncytial Virus (RSV) Infection*, **Targeting Cellular Signalling Pathways in Lung Diseases,** 2, 2021, 501-516.

28. M. Aggarwal & R. K. Plemper, *Structural Insight into Paramyxovirus and Pneumovirus Entry Inhibition*, **Viruses,** 12(3), 2020, 342.

29. L. E. Kuek, & R. J. Lee, *First contact: The Role of Respiratory Cilia in Host-Pathogen Interactions in the Airways*, **American Journal of Physiology-Lung Cellular and Molecular Physiology,** *319*(4), 2020, 603-619.

30. S. Lane, Y. Hilliam & J. M. Bomberger, *Microbial and Immune Regulation of the Gut-Lung Axis during Viral-Bacterial Coinfection*, **Journal of Bacteriology,** 205(1), 2023, 00295-22.

31. F. P. Laenger, N. Schwerk, J. Dingemann, T. Welte, B. Auber, S. Verleden, & D. Jonigk, *Interstitial Lung Disease in Infancy and Early Childhood: A Clinicopathological Primer*, **European Respiratory Review,** 31(163), 2022, 2.

32. S. K. Debnath, M. Debnath & R. Srivastava, *Opportunistic Etiological Agents causing Lung Infections: Emerging need to Transform Lung-Targeted Delivery*, **Heliyon,** 2, 2022 12620.

33. L. E. Kuek & R. J. Lee, *First contact: The Role of Respiratory Cilia in Host-Pathogen Interactions in The Airways*, **American Journal of Physiology-Lung Cellular and Molecular Physiology,** 319(4), 2020, L603-L619.
34. S. Alnajjar, *Therapeutic Efficacy of Antiviral Compounds in the Neonatal Lamb Model of Respiratory Syncytial Virus Infection of Infants with Pathogenesis of Secondary Streptococcus Pneumoniae Infection* (**Doctoral dissertation, Iowa State University**) 2019.

35. S. Eymieux, Y. Rouillé, O. Terrier, K. Seron, E. Blanchard, M. Rosa-Calatrava & P. Roingeard, *Ultrastructural Modifications Induced by SARS-CoV-2 in Vero Cells: A Kinetic Analysis of Viral Factory Formation, Viral Particle Morphogenesis and Virion Release*, **Cellular and Molecular Life Sciences,** 78, 2021, 3565-3576.

36. H. Hopfer, M. C. Herzig, R. Gosert, T. Menter, J. Hench, A. Tzankov & S. E. Miller, *Hunting Coronavirus by Transmission Electron Microscopy–A Guide to SARS-CoV-2-Associated Ultrastructural Pathology in COVID-19 Tissues*, **Histopathology,** 78(3), 2021, 358-370.

37. K. Dicker, A. I. Järvelin, M. Garcia-Moreno & A. Castello, *The Importance of Virion-Incorporated Cellular RNA-Binding Proteins in Viral Particle Assembly and Infectivity*, In **Seminars in Cell & Developmental Biology**, 2021, 108-118.

38. Q. W. Teo, van S. W. Leur & S. Sanyal, *Escaping the Lion's Den: Redirecting Autophagy for Unconventional Release and Spread of Viruses*, **The FEBS Journal**, 288 (13), 2021, 3913-3927.

39. R. Linnakoski, S. Sutela, M. P. Coetzee, T. A. Duong, I. N. Pavlov Y. A., Litovka & E. J. Vainio, *Armillaria Root Rot Fungi Host Single-Stranded RNA Viruses*, **Scientific Reports,** 11(1), 2021, 7336.

40. J. Wang, C. Shi, Q. Xu & H. Yin, SARS-CoV-*2 Nucleocapsid Protein Undergoes Liquid–Liquid Phase Separation into Stress Granules through its N-Terminal Intrinsically Disordered Region*, **Cell discovery,** 7(1), 2021, 5.

41. J. M. Su, M. Z. Wilson, C. E. Samuel & D. Ma, *Formation and Function of Liquid-like Viral Factories in Negative-Sense Single-Stranded RNA Virus Infections*, **Viruses,** *13*(1), 2021, 126.

42. M. C. Pandya, S. M. Callahan, K. G. Savchenko & C. C. Stobart, *A Contemporary View of Respiratory Syncytial Virus (RSV) Biology and Strain-Specific Differences*, **Pathogens,** *8*(2), 2019, 67.

43. J. C. Muñoz-Escalante, A. Comas-García, S. Bernal-Silva, C. D. Robles-Espinoza, G. Gómez-Leal & D. E. Noyola, *Respiratory Syncytial Virus A Genotype Classification based on Systematic Intergenotypic and Intragenotypic Sequence Analysis*. **Scientific Reports,** *9*(1), 2019, 1-12.

44. K. Cantú-Flores, G. Rivera-Alfaro, J. C. Muñoz-Escalante & D. E. Noyola, *Global Distribution of Respiratory Syncytial Virus A and B Infections: A Systematic Review*, **Pathogens and Global Health,** *116*(7), 2022, 398-409.

45. J. M. Yu, Y. H. Fu, X. L. Peng, Y. P. Zheng & J. S. He, *Genetic Diversity and Molecular Evolution of Human Respiratory Syncytial Virus* A and B, **Scientific Reports,** *11*(1), 2021, 12941.

46. B. K. Thielen, E. Bye, X. Wang, S. Maroushek, H. Friedlander, S. Bistodeau & R. Lynfield, *Summer Outbreak of Severe RSV-B Disease, Minnesota, 2017 associated with Emergence of a Genetically Distinct Viral Lineage*, **The Journal *of* Infectious Diseases**, 222(2), 2020, 288-297.

47. S. S. Malekshahi, Y. Samieipour, A. A. Rahbarimanesh, A. Izadi, N. Ghavami, S. Razaghipour & V. Salimi, *Genetic Characterization of G Protein in Respiratory Syncytial Virus ON-1 Genotype in Tehran,* **Future Virology,** *15*(11), 2020, 725-734.

48. U. B. Aamir, M. Salman, N. Nisar, N. Badar, M. M. Alam, J. Ansari & S. S. Z. Zaidi, *Molecular Characterization of Circulating Respiratory Syncytial Virus Genotypes in Pakistani Children, 2010–2013*, **Journal of Infection and Public Health,** *13*(3), 2020, 438-445.

49. H. N. Kim, J. Hwang, S. Y. Yoon, C. S. Lim, Y. Cho, C. K., Lee, & M. H. Nam, *Molecular Characterization of Human Respiratory Syncytial Virus in Seoul, South Korea, During 10 Consecutive Years, 2010–2019*, **Plos One,** 18(4), 2023, 0283873.

50. L. Gimferrer, J. ila, M. Piñana, C. Andrés, J. A. Rodrigo-Pendás, P. Peremiquel-Trillas & A. Antón, *Virological Surveillance of Human Respiratory Syncytial Virus A and B at a Tertiary Hospital in Catalonia (Spain) During Five Consecutive Seasons (2013–2018)*, **Future Microbiology,** 14(5), 2019, 373-381.

51. Y. P. Sun, S. Y. Lei, Y. B. Wang, Y. Z. Wang, H. S. Qiang, Y. F. Yin, & N. S. Xia, *Molecular Evolution of Attachment Glycoprotein (G) and Fusion Protein (F) Genes of Respiratory Syncytial Virus ON1 and BA9 Strains in Xiamen, China*, **Microbiology Spectrum,** 10(2), 2022, 02083-21.

52. C. Hopkins, *Loss of sense of smell as marker of COVID-19 infection*, *Ear, Nose and Throat Surgery Body of United Kingdom, Retrieved 2020.*

53. I. Hosen, A.H. Pakpour, N. Sakib, N. Hussain, F.A.l. Mamun & M.A. Mamun, *Knowledge and Preventive Behaviors Regarding COVID-19 in Bangladesh: A Nationwide Distribution*, **PLoS One,** *16*(5), 2021, 0251151.

54. D. S. Hui, E. I. Azhar, T.A. Madani, F. Ntoumi, R. Kock, O. Dar & E. Petersen, *The Continuing 2019-Ncov Epidemic Threat of Novel Coronaviruses to Global Health—The latest 2019 Novel Coronavirus Outbreak in Wuhan, China*, **International Journal of infectious diseases,** 91, 2020, 264-266.

55. O. Ilesanmi, A. Afolabi. *Perception and Practices during the COVID-19 Pandemic in an Urban Community in Nigeria: A Cross-Sectional Study*, **Peer Journal,** 8, 2020-10038.

56. C. C. Lai, T. P. Shih, W. C. Ko, H. J. Tang & P. R. Hsueh, *Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease-2019 (COVID-19): The Epidemic and the Challenges*, **International Journal of Antimicrobial Agents,** 55(3), 2020, 105924.

57. N. Le Bert, A. T. Tan, K. Kunasegaran, C. Y. Tham, M. Hafezi & A. Bertoletti, *SARS-CoV-2-Specific T Cell Immunity in Cases of COVID-19 and SARS, and Uninfected Controls*, ***Nature,*** *584*(7821), 2020, 457-462.

58. M. Lee M. You, *Psychological and Behavioral Responses in South Korea During the Early Stages of Coronavirus Disease 2019 (COVID-19),* **Int J Environ Res Public Health,** 17(9), 2020, 2977.

59. H. Liua, L.L. Wanga, S.J. Zhaoa, J. Kwak-Kimb, G. Mord, A.H. Liaoa, *Why are Pregnant Women Susceptible to COVID-19, An Immunological Viewpoint,* **J Reprod Immunol**, 139, 2020, 103122.

60. S. K. Lorfa, I. F. Ottu, R. Oguntayo, O. Ayandele, S. O. Kolawole, & P. O. Olapegba, *COVID-19 Knowledge, Risk Perception, and Precautionary Behavior among Nigerians: A Moderated Mediation Approach*, **Frontiers in Psychology,** 11, 2020, 3292.

61. M. Lotfi, M. R. Hamblin & N. Rezaei, COVID-19: *Transmission, Prevention, and Potential Therapeutic Opportunities*, **Clinica Chimica Acta,** 508, 2020, 254– 266.

62. E. Mohamad & A. A. Azlan, *COVID-19 and Communication Planning for Health Emergencies, Jurnal Komunikasi:* **Malaysian Journal of Communication,** 36(1), 2020, 1-2.

63. J. B. Nachega, R. Atteh, C. Ihekweazu, N.A. Sam-Agudu, P. Adejumo, & P. H. Kilmarx, *Contact Tracing and the COVID-19 Response in Africa: Best Practices, Key Challenges, and Lessons Learned from Nigeria, Rwanda, South Africa, and Uganda*, **The American Journal of Tropical Medicine and Hygiene,** 104(4), 2021, 1179.

64. H.A. Naseef, L.S. Hadba & L.A. Humos, *Knowledge, Attitudes and Practices about Coronavirus Disease (COVID-19) Among Birzeit University Students: A Cross-Sectional Study,* **Journal of Public Health**, 30(1), 2021, 22.

65. *NCDC. COVID-19 Nigeria—Nigeria Centre for Disease Control 2020.*

66. P. Norman, S. Wilding & M. Conner. *Reasoned Action Approach and Compliance with Recommended Behaviours to Prevent the Transmission of the SARS-CoV-2 Virus in the UK,* **British Journal of Health Psychology,** 25, 2020, 1006– 1019.

67. E.U. Nwonwu, E.N. Ossai, C.D. Umeokonkwo & I.B. Ituma, *Knowledge and Preventive Practice to COVID-19 among Household Heads in Enugu Metropolis, South-East Nigeria,* **The Pan African Medical Journal**, 37, 2020, 2-3.

68. O. E. Omotoso, *Contributory Role of SARS-CoV-2 Genomic Variations and Life*, **The Pan African Medical Journal,** 100, 2020, 123.

69. O. E. Omotoso, E.F. Omotoso, K.O. Paimo, J. O. Teibo & A. O. Olagunju, *Knowledge and Adherence to COVID-19 Preventive Measures: A Continental Review,* **Sudan Journal of Medical Sciences,** 16(3), 2021, 371-385.

70. S. Ozdemir, S. Ng, I. Chaudhry & E. A. Finkelstein, *Adoption of Preventive Behaviour Strategies and Public Perceptions about COVID-19 in Singapore,* **International Journal of Heal Policy Management**, 2, 2020,1-3.

71. M. K. Al-Hanawi, K. Angawi, N. Alshareef, A. Qattan, W. M. Kattan & O. Alsharqi, *Knowledge, Attitude and Practice Toward COVID-19 Among the Public in the Kingdom of Saudi Arabia: A Cross-Sectional Study,* **Frontiers in Public Health,** 8, 2020, 217.

72. I. Ayouni, J. Maatoug, W. Dhouib, N. Zammit, S.B. Fredj & H. Ghannem, *Effective Public Health Measures to Mitigate the Spread of COVID-19: A Systematic Review,* **BMC Public Health,** 21, 2021, 1015.

73. Z.N. Azene, M.W. Merid, A.G. Muluneh, D.M. Geberu, G.M. Kassa & M.K. Yenit, *Adherence Towards COVID-19 Mitigation Measures and Its Associated Factors among Gondar City Residents: A Community-Based Cross-Sectional Study in Northwest Ethiopia,* ***PLoS ONE,*** 15(12), 2020, 33378332.

74. Y. Bai, L. Yao, T. Wei, F. Tian, D.Y. Jin, L. Chen & M. Wang, *Presumed Asymptomatic Carrier Transmission of COVID*-19, **Jama,** 323(14), 2020, 1406-1407.

75. R. Bayomi, *Effect of Teaching Guidelines on Knowledge, Attitudes, and Practices Regarding COVID 19 among the First Year Nursing Students*, **Assiut Scientific Nursing Journal, 9** (25), 2021, 38-47.

76. J. A. Belser & T. M. Tumpey, *The 1918 flu, 100 Years Later*. ***Science,*** 359(6373), 2019, 255-255.

77. S. K. Brooks, R.K. Webster, L.E. Smith, L. Woodland, S. Wessely & G. J. Rubin, *The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence*, ***The Lancet,*** 395(10227), 2020, 912-920.

78. C. C. Lai, T. P. Shih, W. C. Ko, H. J. Tang & P. R. Hsueh, *Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease-2019 (COVID-19): The Epidemic and the Challenges,* **International Journal of Antimicrobial Agents,** 55(3), 2020, 105924.

79. N. Le Bert, A.T. Tan, K. Kunasegaran, C.Y. Tham, M. Hafezi & A. Bertoletti, *SARS-CoV-2-Specific T Cell Immunity in Cases of COVID-19 and SARS, and Uninfected Controls*, ***Nature,*** 584(7821), 2020, 457-462.

80. M. Lee & M. You. *Psychological and Behavioral Responses in South Korea During the Early Stages of Coronavirus Disease 2019 (COVID-19)*, **Int J Environ Res Public Health**, 17(9), 2020, 2977.

81. S. K. Lorfa, I. F. Ottu, R. Oguntayo, O. Ayandele, S.O. Kolawole & P. O. Olapegba, *COVID-19 Knowledge, Risk Perception, and Precautionary Behavior among Nigerians: A Moderated Mediation Approach,* **Frontiers in Psychology,** 11, 2020, 3292.

82. M. Lotfi, M.R. Hamblin, & N. Rezaei, COVID-19: *Transmission, Prevention, and Potential Therapeutic Opportunities*, **Clinica Chimica Acta,** 508**,** 2020, 254– 266.

83. S. McNab, L. A. Ha, Do, V. Clifford, N. W. Crawford, A. Daley, K. Mulholland & D. Wurze, *Changing Epidemiology of Respiratory Syncytial Virus in Australia—Delayed Re-Emergence in Victoria Compared to Western Australia/New South Wales (WA/NSW) After Prolonged Lock-Down for Coronavirus Disease 2019 (COVID-19),* **Clinical Infectious Diseases,** *73*(12), 2021, 2365-2366.

84. L. Staadegaard, S. Caini, S. Wangchuk, B. Thapa, W. A. F. de Almeida, F. C. de Carvalho & J. Paget, *The Global Epidemiology of RSV in Community and Hospitalized Care: Findings from 15 Countries, In* **Open Forum Infectious Diseases** *(Vol. 8, No. 7, p. ofab159), US: Oxford University Press 2021.*

85. M.D. Takashima, K. Grimwood, P. D. Sly S.B. Lambert, K.J. Chappell, D. Watterson, & R.S. Ware, *Epidemiology of Respiratory Syncytial Virus in a Community Birth Cohort of Infants in the First 2 Years of Life,* **European Journal of Pediatrics,** 2021, 180, 2125-2135.

86. C. Azzari, E. Baraldi, P. Bonanni, E. Bozzola, A. Coscia, M. Lanari & F. Mosca, *Epidemiology and Prevention of Respiratory Syncytial Virus Infections in Children in Italy*, **Italian Journal of Pediatrics,** 47, 2021, 1-12.

87. K. C. Halabi, L. Saiman & P. Zachariah, The Epidemiology of Respiratory Syncytial Virus in New York City During the Coronavirus Disease-2019 Pandemic Compared with Previous Years, **The Journal of Pediatrics,** 242, 2022, 242-244.

88. M.L. Jackson, E. Scott, J. Kuypers, A.K. Nalla, P. Roychoudury & H.Y. Chu, *Epidemiology of Respiratory Syncytial Virus Across Five Influenza Seasons among Adults and Children One Year of Age and Older—Washington State, 2011/2012–2015/2016*, **The Journal of Infectious Diseases,** *223*(1), 2021, 147-156.

89. J. van Summeren, A. Meijer, G. Aspelund, J.S. Casalegno, G. Erna, U. Hoang & J. Paget, *Low Levels of Respiratory Syncytial Virus Activity in Europe During the 2020/21 Season: What Can We Expect In The Coming Summer And Autumn/Winter?*. **Eurosurveillance,** *26*(29), 2021, 2100639.

90. M. Bardsley, R.A. Morbey, H.E. Hughes, C.R. Beck, C.H. Watson, H. Zhao & A.J. Elliot, *Epidemiology of Respiratory Syncytial Virus in Children Younger than 5 Years in England During the COVID-19 Pandemic, Measured by Laboratory, Clinical, and Syndromic Surveillance: A Retrospective Observational Study*, **The Lancet Infectious Diseases,** *23*(1), 2023, 56-66.

91. M. Suryadevara, & J. B. Domachowske, *Epidemiology and Seasonality of Childhood Respiratory Syncytial Virus Infections in the Tropics,* **Viruses,** 13(4), 2021, 696.

92. L. Hernández-Rivas, T. Pedraz, C. Calvo, I. San Juan & A. Robustillo, *Respiratory Syncytial Virus Outbreak During the Covid-19 Pandemic, How Has it Changed?* **Enfermedades Infecciosasy Microbiología Clínica**, 2, 2021, 3-4.

93. D.E. Tabor, F. Fernandes, A.C. Langedijk, D. Wilkins, R.J. Lebbink, A. Tovchigrechko & M. E. Abram, *Global Molecular Epidemiology of Respiratory Syncytial Virus from the 2017− 2018 INFORM-RSV Study*, **Journal of Clinical Microbiology,** 59(1), 2020, 01828-20.

94. K.W. Yun, E.H. Choi & H.J. Lee, *Molecular Epidemiology of Respiratory Syncytial Virus for 28 Consecutive Seasons (1990-2018) and Genetic Variability of the Duplication Region in the G Gene of Genotypes ON1 and BA in South Korea*, **Archives of Virology,** 165(5), 2020, 1069-1077.

95. F. Barbati, M. Moriondo, L. Pisano, E. Calistri, L. Lodi, S. Ricci & C. Azzari, *Epidemiology of Respiratory Syncytial Virus-Related Hospitalization Over A 5-Year Period in Italy: Evaluation of Seasonality and Age Distribution before Vaccine Introduction,* **Vaccines,** 8(1), 2020, 15.

96. B. Resch, C. Puchas, E. Resch & B. Urlesberger, *Epidemiology of Respiratory Syncytial Virus–Related Hospitalizations and The Influence of Viral Coinfections in Southern Austria in a 7-Year Period,* **The Pediatric Infectious Disease Journal,** 39(1), 2020, 12-16.

97. K.C. Halabi, L. Saiman & P. Zachariah, *The Epidemiology of Respiratory Syncytial Virus in New York City During The Coronavirus Disease-2019 Pandemic Compared with Previous Years,* **The Journal of Pediatrics**, 242, 2022, 242-244.

98. S. McNab, L.A. Ha Do, V. Clifford, N.W. Crawford, A. Daley, K. Mulholland & D. Wurzel, *Changing Epidemiology of Respiratory Syncytial Virus in Australia—Delayed Re-Emergence in Victoria Compared to Western Australia/New South Wales (WA/NSW) After prolonged lock-down for coronavirus disease 2019 (COVID-19),* **Clinical Infectious Diseases,** 73(12), 2021, 2365-2366.

99. M. Bardsley, R.A. Morbey, H.E. Hughes, C.R. Beck, C.H. Watson, H. Zhao, & A. J. Elliot, *Epidemiology of Respiratory Syncytial Virus in Children Younger Than 5 Years in England During the COVID-19 Pandemic, Measured by Laboratory, Clinical, and Syndromic Surveillance: A Retrospective Observational Study,* **The Lancet Infectious Diseases,** 23(1), 2023, 56-66.

100. C. Wei, K. Tolksdorf, S. Hirve, E. Schuler, W. Zhang, W. Haas & S. Buda, "*Evaluation of using ICD-10 Code Data for Respiratory Syncytial Virus Surveillance"* **Influenza and Other Respiratory Viruses,** 14,(6), 2020, 630-637.

101. L. Pellegrinelli, C. Galli, L. Bubba, D. Cereda, G. Anselmi, S. Binda & E. Pariani, *Respiratory Syncytial Virus in Influenza-Like Illness Cases: Epidemiology and Molecular Analyses of Four Consecutive Winter Seasons (2014-2015/2017-2018) in Lombardy (Northern Italy),* **Journal of Medical Virology,** 92(12), 2020, 2999-3006.

102. F.H. Varela, M. C. Scotta, M. Polese-Bonatto I.T.S. Sartor, C. F. Ferreira, I.R. Fernandes & COVID a Study Group, *Absence of Detection of RSV and Influenza During the COVID-19 Pandemic in a Brazilian Cohort: Likely Role of Lower Transmission in the Community,* **Journal of Global Health**, 2, 2021, 11.

103. L. Staadegaard, S. Caini, S. Wangchuk, B. Thapa, W.A.F. de Almeida, F.C. de Carvalho & J. Paget, *Defining the Seasonality of Respiratory Syncytial Virus around the World: National and Subnational Surveillance Data from 12 Countries*, **Influenza and Other Respiratory Viruses,** 15(6), 2021, 732-741.

104. M.N. Billard, P. M. van de, B.Ven. Baraldi, L. Kragten-Tabatabaie, L. J. Bont & J. G. Wildenbeest, *International Changes in Respiratory Syncytial Virus (RSV) Epidemiology During The COVID-19 Pandemic: Association with School Closures*, **Influenza and Other Respiratory Viruses,** 16(5), 2022, 926-936.

105. P.A. Alvares, *SARS-CoV-2 and Respiratory Syncytial Virus Coinfection in Hospitalized Pediatric Patients*, **The Pediatric Infectious Disease Journal**, 40(4), 2021, 164-166.

106. L.A. Vianna, M.M. Siqueira, L. P. Volpini, I. D. Louro & P.C. Resende, *Seasonality, Molecular Epidemiology, and Virulence of Respiratory Syncytial Virus (RSV): A Perspective into the Brazilian Influenza Surveillance Program,* **Plos One,** 16(5), 2021, 0251361.

107. V.M. Pscheidt, T.S. Gregianini, L.G. Martins & A.B.G.D. Veiga, *Epidemiology of Human Adenovirus Associated with Respiratory Infection in Southern Brazil,* **Reviews In Medical Virology**, 31(4), 2021, 2189.

109. A. Amoo. *Respiratory Syncytial Virus Infection among Children in Lagos, Nigeria,* **J Clin Immunol Microbiol,** 2(1), 2021, 1-11.

110. O.O. Idris & O.M. Kolawole, *Seroprevalence and Molecular Characterization of Human Respiratory Syncytial Virus and Human Adenovirus among Children in Ado-Ekiti, Nigeria,* **Journal of Medical Virology,** 94(6), 2022, 2548-2557.

111. I. Kuitunen & M. Renko, *Lessons to Learn from The Current Pandemic for Future Non-Pharmaceutical Interventions against The Respiratory Syncytial Virus–Nationwide Register-Study in Finland,* **Infectious Diseases**, 53(6), 2021, 476-478.

112. A.C. Vittucci, L. Piccioni, L. Coltella, C. Ciarlitto, L. Antilici, E. Bozzola & A. Villani, *The Disappearance of Respiratory Viruses in Children During The COVID-19 Pandemic*, **International Journal of Environmental Research and Public Health,** 18(18), 2021, 9550.

113. J.S. Cruz, L.K. de Souza Luna, V. R. G. Alves, D.D. Conte & N.C.J. Bellei, *Viral Load of Respiratory Syncytial Virus Among Children from Primary Care and Hospital Settings Admitted to A University Hospital in Brazil (2009-2013)*, **Journal of Medical Virology,** 93(6), 2021, 3397-3400.

114. J.S. Casalegno, D. Ploin, A. Cantais, E. Masson, E. Bard, M. Valette & Y. Gillet *Characteristics of The Delayed Respiratory Syncytial Virus Epidemic, 2020/2021, Rhône Loire, France,* **Eurosurveillance,** 26(29), 2021, 2100630.

115. J. van Summeren, A. Meijer, G. Aspelund, J. S. Casalegno, G. Erna, U. Hoang & J. Paget, *Low Levels of Respiratory Syncytial Virus Activity in Europe During The 2020/21 Season: What Can We Expect in The Coming Summer and Autumn/Winter?,* **Eurosurveillance,** 26 (29), 2021, 2100639.

116. D.K. Yeoh, D.A. Foley, C.A. Minney-Smith, A.C. Martin, A. O. Mace, C. T. Sikazwe & H. C. Moore, *Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children During The 2020 Australian Winter*, **Clinical Infectious Diseases,** 72(12), 2021, 2199-2202.

117. D.K. Yeoh, D.A. Foley, C.A. Minney-Smith, A.C. Martin, A.O. Mace, C.T. Sikazwe, & H.C. Moore, *Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children During the 2020 Australian Winte*r, **Clinical Infectious Diseases,** 72(12), 2021, 2199-2202.

118. S. Tempia, S. Walaza, J. N. Bhiman, M.L. McMorrow, J. Moyes, T. Mkhencele & C Cohen. *Decline of Influenza and Respiratory Syncytial Virus Detection in Facility-Based Surveillance During The COVID-19 Pandemic, South Africa, January to October 2020*, **Eurosurveillance,** 26(29), 2021, 2001600.

119. S. Bianchini, E. Silvestri, A. Argentiero, V. Fainardi, G. Pisi & S. Esposito, *Role of Respiratory Syncytial Virus in Pediatric Pneumonia,* **Microorganisms,** 8(12), 2020, 2048.

120. C. S. Arriola, L. Kim, G. Langley, E. J. Anderson, K. Openo, A.M. Martin & S. S. Chaves, *Estimated Burden of Community-Onset Respiratory Syncytial Virus–Associated Hospitalizations among Children Aged< 2 Years in the United States, 2014–15,* **Journal of the Pediatric Infectious Diseases Society**, 9(5), 2020, 587-595.

121. D.A. Schwartz & A. Dhaliwal, *Infections in Pregnancy with COVID-19 and Other Respiratory RNA Virus Diseases are Rarely, If Ever, Transmitted to the Fetus: Experiences with Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and influenza,* **Archives of Pathology & Laboratory Medicine,** 144(8), 2020, 920-928.

122. M. Ujiie, S. Tsuzuki, T. Nakamoto & N. Iwamoto, *Resurgence of Respiratory Syncytial Virus Infections During COVID-19 Pandemic, Tokyo, Japan,* **Emerging Infectious Diseases,** 27(11), 2021, 2969.

123. L. Hatter, A. Eathorne, T. Hills, P. Bruce & R. Beasley, *Respiratory Syncytial Virus: Paying the Immunity Debt with Interest*, **The Lancet Child & Adolescent Health,** 5(12), 2021, 44-45.

124. A. Rybak, C. Levy, C. Jung, S. Béchet, C. Batard, F. Hassid & R. Cohen, *Delayed Bronchiolitis Epidemic in French Primary Care Setting Driven by Respiratory Syncytial Virus: Preliminary Data from the Oursyn Study, March 2021,* **The Pediatric Infectious Disease Journal,** 40(12), 2021, 511-514.

125. J. van Summeren, A. Meijer, G. Aspelund, J. S. Casalegno, G. Erna, U. Hoang & J. Paget, *Low Levels of Respiratory Syncytial Virus Activity in Europe During the 2020/21 Season: What Can We Expect In The Coming Summer and Autumn/Winter,* **Eurosurveillance**, 26(29), 2021, 2100639.

126. T.C. Williams, I. Sinha, I.G. Barr & M. Zambon, *Transmission of Paediatric Respiratory Syncytial Virus and Influenza In The Wake of The Covid-19 Pandemic*, **Eurosurveillance,** 26(29), 2021, 2100186.

127. K. M. Edwards, *The Impact of Social Distancing for Severe Acute Respiratory Syndrome Coronavirus 2 On Respiratory Syncytial Virus and Influenza Burden,* **Clinical Infectious Diseases,** 72(12), 2021, 2076-2078.

128. J.H. Kim, Y.H. Roh, J.G. Ahn, M.Y. Kim, K. Huh, J. Jung & J.M. Kang, *Respiratory Syncytial Virus and Influenza Epidemics Disappearance in Korea during the 2020–2021 Season of COVID-19,* **International Journal of Infectious Diseases,** 110, 2021, 29-35.

129. D.K. Yeoh, D.A. Foley, C.A. Minney-Smith, A.C. Martin, A.O. Mace, C.T. Sikazwe, & H.C. Moore, *Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children during the 2020 Australian Winter*, **Clinical Infectious Diseases,** 72(12), 2021, 2199-2202.

130. D.A. Foley, D.K. Yeoh, C.A. Minney-Smith, A.C. Martin, A.O. Mace, C.T. Sikazwe, & C.C. Blyth, *The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children following the Reduction of Coronavirus Disease 2019–Related Public Health Measures,* **Clinical Infectious Diseases,** 73(9), 2021, 2829-2830.

131. K. Wagatsuma, I. S. Koolhof, Y. Shobugawa & R. Saito, *Decreased Human Respiratory Syncytial Virus Activity during the COVID-19 Pandemic in Japan: An Ecological Time-series Analysis*, **BMC Infectious Diseases,** 21, 2021, 1-13.

132. I. Kuitunen & M. Renko, *Lessons to Learn from The Current Pandemic for Future Non-Pharmaceutical Interventions against the Respiratory Syncytial Virus–Nationwide Register-Study in Finland,* **Infectious Diseases,** 53(6), 2021, 476-478.

133. M.W. Opek, Y. Yeshayahu, A. Glatman-Freedman, Z. Kaufman, N. Sorek & Nissimov B.T, *Delayed Respiratory Syncytial Virus Epidemic in Children After Relaxation of COVID-19 Physical Distancing Measures, Ashdod, Israel*, **Eurosurveillance,** 26(29), 2021, 2100706.

134. J. S. Casalegno, D. Ploin, A. Cantais, E. Masson, E. Bard, M. Valette & Y. Gillet, *Characteristics of the Delayed Respiratory Syncytial Virus Epidemic, 2020/2021, Rhône Loire, France,* **Eurosurveillance,** 26(29), 2021, 2100630.

135. J.B. Domachowske, E.J. Anderson & M. Goldstein, *The Future of Respiratory Syncytial Virus Disease Prevention and Treatment*, **Infectious Diseases and Therapy**, 10, 2021 47-60.

136. S. McNab, L.A. Ha Do, V. Clifford, N.W. Crawford, A. Daley, K. Mulholland & D. Wurzel, *Changing Epidemiology of Respiratory Syncytial Virus in Australia—Delayed Re-Emergence in Victoria Compared to Western Australia/New South Wales (WA/NSW) After Prolonged Lock-Down for Coronavirus Disease 2019 (COVID-19)*, **Clinical Infectious Diseases,** 73(12), 2021, 2365-2366.

137. T. Tenenbaum, M. Doenhardt, N. Diffloth, R. Berner & J. P. Armann, *High Burden of RSV Hospitalizations in Germany 2021–2022***, Infection,** 50(6), 2022, 1587-1590.

138. P. Srikantiah, P. Vora, & K.P. Klugman, *Assessing the Full Burden of Respiratory Syncytial Virus in Young Infants in Low-and Middle-Income Countries: The Importance of Community Mortality Studies*, **Clinical Infectious Diseases,** 73(3), 2021, 177-179.

139. E. Thomas, J. M. Mattila, P. Lehtinen, T. Vuorinen, M. Waris & T. Heikkinen, *Burden of Respiratory Syncytial Virus Infection during the First Year of Life,* **The Journal of Infectious Diseases,** 223(5), 2021, 811-817.

140. C. Demont, N. Petrica, I. Bardoulat, S. Duret, L. Watier, A. Chosidow & M. Lemaitre, *Economic and Disease Burden of RSV-Associated Hospitalizations in Young Children in France, from 2010 through 2018*, **BMC Infectious Diseases,** 21(1), 2021, 730.

141. S. P. Andeweg, R. M. Schepp, J. van de Kassteele, L. Mollema, G. A. Berbers & van M. Boven, *Population-Based Serology Reveals Risk Factors for RSV Infection in Children Younger than 5 years.* **Scientific Reports,** 11(1), 2021, 1-8.

142. Y. Li, E.K. Johnson, T. Shi, H. Campbell, S.S. Chaves, C. Commaille-Chapus & H. Nair, *National Burden Estimates of Hospitalisations for Acute Lower Respiratory Infections Due to Respiratory Syncytial Virus in Young Children in 2019 among 58 Countries: A Modelling Study,* **The Lancet Respiratory Medicine,** 9(2), 2021, 175-185.

143. A.L. von Hammerstein, C. Aebi, F. Barbey, C. Berger, M. Buettcher, C. Casaulta & J. Trück, *Interseasonal RSV Infections in Switzerland-Rapid Establishment of a Clinician-Led National Reporting System (RSV EpiCH),* **Swiss Medical Weekly**, 151, 2021,30057.

144. A.S. Ginsburg & P. Srikantiah, *Respiratory Syncytial Virus: Promising Progress against a Leading Cause of Pneumonia,* **The Lancet Global Health,** 9(12), 2021, 1644-1645.

145. J.J.G.T. Van Summeren, C. Rizzo, M. Hooiveld, J.C. Korevaar, J.M.T. Hendriksen, M. L.A. *Dückers & J. Paget, Evaluation of a Standardised Protocol to Measure the Disease Burden of Respiratory Syncytial Virus Infection in Young Children in Primary Care,* **BMC Infectious Diseases,** 21(1), 2021, 1-10.

146. M.P. Nowalk, H.D'Agostino, K. Dauer, M. Stiegler, R.K. Zimmerman & G.K. Balasubramani, *Estimating the Burden of Adult Hospitalized RSV Infection including Special Populations.* **Vaccine,** 40(31), 2022, 4121-4127.

147. R.S. Linssen, R.A. Bem, B. Kapitein, K.O. Rengerink, M.H. Otten, B. den Hollander, & PICE Study Group, M. Wösten-van Asperen Roelie, H. Klein Richard, C.J Kneyber Martin Kuiper Jan Willem Verlaat Carin van Heerde Mar,c A. Riedijk Maaike, A. van Waardenburg Dick, *Burden of Respiratory Syncytial Virus Bronchiolitis on the Dutch Pediatric Intensive Care Units,* **European Journal of Pediatrics,** 180(10), 2021, 3141-3149.

148. J. B. Domachowske, E.J. Anderson & M. Goldstein, *The Future of Respiratory Syncytial Virus Disease Prevention and Treatment,* **Infectious Diseases and Therapy,** *10*, 2021, 47-60.

149. M. Young & L. *Smitherman, Socioeconomic Impact of RSV Hospitalization,* **Infectious Diseases and Therapy,** 10, 2021, 35-45.

150. A. Chatterjee, K. Mavunda & L.R. Krilov, *Current State of Respiratory Syncytial Virus Disease and Management,* **Infectious Diseases and Therapy,** 10, 2021, 5-16.

151. Z. Zheng, V.E. Pitzer, E.D. Shapiro, L.J., Bont & D.M. Weinberger, *Estimation of the Timing and Intensity of Reemergence of Respiratory Syncytial Virus following the COVID-19 Pandemic in the U.S.,* **JAMA Network Open,** 4(12), 2021, 2141779-2141779.

152. T. Shi, A. Denouel, A.K. Tietjen, I. Campbell, E. Moran, X. Li, & H. Nair, *Global Disease Burden Estimates of Respiratory Syncytial Virus–Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis* **The Journal of Infectious Diseases**, 222(7), 2020, 577-583.

153. D.A. Schwartz & A. Dhaliwal. *Infections in Pregnancy with COVID-19 and other Respiratory RNA Virus Diseases are Rarely, If ever, Transmitted to the Fetus: Experiences with Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and Influenza.* **Archives of Pathology & Laboratory Medicine,** 144(8), 2020, 920-928.

154. I. Kuitunen & M. Renko. *Lessons to Learn from the Current Pandemic for Future Non-Pharmaceutical Interventions against the Respiratory Syncytial Virus–Nationwide Register-Study in Finland*, **Infectious Diseases**, 53(6), 2021, 476-478.

155. S. Pappa, K. Haidopoulou, C. Zarras, E. Theodorakou, E. Papadimitriou, E. Iosifidis & A. Papa, *Early Initiation of the Respiratory Syncytial Virus Season in 2021–2022, Greece,* **Journal of Medical Virology,** 94(7), 2022, 3453-3456.

156. F.H. Varela, M.C. Scotta, M. Polese-Bonatto, I.T.S. Sartor, C.F. Ferreira, I.R. Fernandes & COVID A Study Group, *Absence of Detection of RSV and Influenza during the COVID-19 Pandemic in a Brazilian Cohort: likely Role of Lower Transmission in the Community,* **Journal of Global Health,** 11, 2021, 1.

157. P. Stamm, I. Sagoschen, K. Weise, B. Plachter, T. Münzel, T. Gori & M. Vosseler, *Influenza and RSV Incidence during COVID-19 Pandemic—An Observational Study From In-Hospital Point-of-Care Testing*, **Medical Microbiology and Immunology**, 210, 2021, 277-282.

158. J.H. Kim, Y.H. Roh, J.G. Ahn, M.Y. Kim, K. Huh, J. Jung & J.M. Kang, *Respiratory Syncytial Virus and Influenza Epidemics Disappearance in Korea during the 2020–2021 Season of COVID-19*, **International Journal of Infectious Diseases,** 110, 2021, 29-35.

159. H. E. Groves, P. P. Piché-Renaud, A. Peci, D.S. Farrar, S. Buckrell, C. Bancej & S.K. Morris, *The Impact of the COVID-19 Pandemic on Influenza, Respiratory Syncytial Virus, and Other Seasonal Respiratory Virus Circulation in Canada: A Population-Based Study,* **The Lancet Regional Health-Americas,** 1, 2021, 100015.

160. T.C. Williams, I. Sinha, I.G. Barr, & M. Zambon, *Transmission of Paediatric Respiratory Syncytial Virus and Influenza in the wake of the COVID-19 Pandemic,* **Eurosurveillance,** 26(29), 2021, 2100186.

161. S. J. Olsen, A. K. Winn, A. P. Budd, M.M. Prill, J. Steel, C. M. Midgley & B. J. Silk, *Changes in Influenza and Other Respiratory Virus Activity during the COVID-19 Pandemic—United States, 2020–2021*, **Morbidity and Mortality Weekly Report,** 70(29), 2021, 1013.

162. D.K. Yeoh, D.A. Foley, C. A. Minney-Smith, A. C. Martin, A. O. Mace, C. T. Sikazwe & H.C. Moore, *Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children during the 2020 Australian Winter,* **Clinical Infectious Diseases,** 72(12), 2021, 2199-2202.

163. E.C.M. Leung, V.C.Y. Chow, M.K.P. Lee, K.P.S. Tang, D.K.C. Li & R.W.M. Lai, *Evaluation of the Xpert Xpress SARS-CoV-2/Flu/RSV Assay for Simultaneous Detection of SARS-CoV-2, Influenza A and B Viruses, and Respiratory Syncytial Virus in Nasopharyngeal Specimens* **Journal of Clinical Microbiology,** 59(4), 2021, 02965-20.

164. T.Y. Kim, J.Y. Kim, H.J. Shim, S.A. Yun, J.H. Jang, H.J. Huh & N.Y. Lee, *Comparison of the PowerChek SARS-CoV-2, Influenza A&B, RSV Multiplex Real-Time PCR Kit and BioFire Respiratory Panel 2.1 for Simultaneous Detection of SARS-CoV-2, Influenza A and B, and Respiratory Syncytial Virus,* **Journal of Virological Methods,** 298, 2021 114304.

165. T. Ohnishi & Y. Kawano, *Resurgence of Respiratory Syncytial Virus Infection during An Atypical Season in Japan,* **Journal of the Pediatric Infectious Diseases Society,** *10*(10), 2021, 982-983.

166. H.H. Mostafa, K.C. Carroll, R. Hicken, G.J. Berry, R. Manji, E. Smith & M.J. Loeffelholz, *Multicenter Evaluation of the Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV Test*, **Journal of Clinical Microbiology,** 59(3), 2021, 02955-20.

167. H.Y. Chung, M.J. Jian, C.K. Chang, J.C. Lin, K.M. Yeh, C.W. Chen & H.S. Shang, *Novel Dual Multiplex Real-Time RT-PCR Assays for the Rapid Detection of SARS-CoV-2, Influenza A/B, and Respiratory Syncytial Virus using the BD MAX Open System,* **Emerging Microbes & Infections,** 10(1), 2021, 161-166.

168. F.H. Varela, M.C. Scotta, M. Polese-Bonatto, I.T.S. Sartor, C.F. Ferreira, I.R. Fernandes & COVIDa study group, *Absence of Detection of RSV and Influenza during the COVID-19 Pandemic in a Brazilian Cohort: Likely Role of Lower Transmission in the Community,* **Journal of Global Health,** 11, 2021, 3.

169. J.A. Mazet, B.N. Genovese, L.A. Harris, M. Cranfield, J.B. Noheri, J.F. Kinani & K. V. Gilardi, *Human Respiratory Syncytial Virus Detected in Mountain Gorilla Respiratory Outbreaks,* **EcoHealth,** 17, 2020, 449-460.

170. Y. Kang, T. Ohnishi, K. Yutaka, T. Kunikata, & K. Ichihashi, *Decrease in Pediatric Inpatients with Respiratory Syncytial Virus Infection during Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic,* **Pediatrics International,** 64(1), 2022, 1-2.

171. M. Stokstad, T.B. Klem, M. Myrmel, V.S. Oma, I. Toftaker, O. Østerås & A. Nødtvedt, *Using Biosecurity measures to Combat Respiratory Disease in Cattle: The Norwegian Control Program for Bovine Respiratory Syncytial Virus and Bovine Coronavirus,* **Frontiers in Veterinary Science,** 7, 2020, 167.

172. A.R. Branche, L. Saiman, E.E. Walsh, A.R. Falsey, W.D. Sieling, W. Greendyke & L. Finelli, *Incidence of Respiratory Syncytial Virus Infection among Hospitalized Adults, 2017–2020,* **Clinical Infectious Diseases,** 74(6), 2022, 1004-1011.

173. M. W. Opek, Y. Yeshayahu, A. Glatman-Freedman, Z. Kaufman, N. Sorek, & Brosh-T. Nissimov, *Delayed Respiratory Syncytial Virus Epidemic in Children After Relaxation of COVID-19 Physical Distancing Measures, Ashdod, Israel, 2021***, Eurosurveillance,** 26(29), 2021, 2100706.

174. A.C. Teirlinck, E.K. Broberg, A.S. Berg, H. Campbell, R.M. Reeves, A. Carnahan & T.K. Fischer, *Recommendations for Respiratory Syncytial Virus Surveillance at the National Level*, **European Respiratory Journal,** 58(3), 2021, 1.

175. E. C. M. Leung, V. C. Y. Chow, M. K. P. Lee, K. P. S. Tang, D. K. C. Li & R. W. M. Lai, *Evaluation of the Xpert Xpress SARS-CoV-2/Flu/RSV Assay for Simultaneous Detection of SARS-CoV-2, Influenza A and B Viruses, and Respiratory Syncytial Virus in Nasopharyngeal Specimens,* **Journal of Clinical Microbiology,** 59(4), 2021, 02965-20.

176. A.C. Teirlinck, E.K. Broberg, A. S. Berg, H. Campbell, R. M. Reeves, A. Carnahan & T. K. Fischer, *Recommendations for Respiratory Syncytial Virus Surveillance at the National Level,* **European Respiratory Journal,** 58(3), 2021, 2.

177. M.W. Opek, Y. Yeshayahu, A. Glatman-Freedman, Z. Kaufman, N. Sorek & Brosh-T. Nissimov, *Delayed Respiratory Syncytial Virus Epidemic in Children after Relaxation of COVID-19 Physical Distancing Measures, Ashdod, Israel,* **Eurosurveillance,** 26(29), 2021, 2100706.

178. F. Wolters, M. Grünberg, M. Huber, H.H. Kessler, F. Prüller, L. Saleh & W. J. Melchers*, European Multicenter Evaluation of Xpert® Xpress SARS-CoV-2/Flu/RSV test*, **Journal of Medical Virology,** 93(10), 2021, 5798-5804.

179. K. R. Kumar, S. S. Mufti, V. Sarathy, D. Hazarika & R. Naik, *An Update on Advances in COVID-19 Laboratory Diagnosis and Testing Guidelines in India*. **Frontiers in Public Health,** 9, 2021, 568603.

180. M.J. Jian, H.Y. Chung, C.K. Chang, J.C. Lin, K.M. Yeh, C.W. Chen & H.S. Shang, *Clinical Comparison of Three Sample-to-Answer Systems for Detecting SARS-CoV-2 in B. 1.1. 7 Lineage Emergence,* **Infection and Drug Resistance**, 3, 2021, 3255-3261.

181. J. A. Buendía & D. G. Patiño, *Costs of Respiratory Syncytial Virus Hospitalizations in Colombia*, **PharmacoEconomics-Open,** 5, 2021, 71-76.

182. T. Miyama, N. Iritani, T. Nishio, T. Ukai, Y. Satsuki, H. Miyata & K. Kobayashi *Seasonal Shift in Epidemics of Respiratory Syncytial Virus Infection in Japan,* **Epidemiology & Infection,** 149, 2021, 1-2.

183. K.T. Franck, U.V. Schneider, C.M. Ma, D. Knudsen & G. Lisby, *Evaluation of Immuview RSV Antigen Test (SSI siagnostica) and BinaxNOW RSV card (alere) for Rapid Detection of Respiratory Syncytial Virus in Retrospectively and Prospectively Collected Respiratory Samples*, **Journal of Medical Virology,** 92(12), 2020, 2992-2998.

184. A. M. Nathan, C.S.J. Teh, K.A. Jabar, B.T. Teoh, A. Tangaperumal, C. Westerhout & J. A. de Bruyne, *Bacterial Pneumonia and its Associated Factors in Children from a Developing Country: A Prospective Cohort Study,* **PloS One,** 15(2), 2020, 0228056.

185. E. M. E. M. Earle's, *Minimum Essential Medium, & PBS, P. B. S. Specimen Collection, Storage, and Transportation 2020.*

186. J. J. Voermans, D. G. Mulders, S. D. Pas, M. P. Koopmans, A. A. van der Eijk & R, Molenkamp. *Performance Evaluation of the Panther Fusion® Respiratory Tract Panel*, **Journal of Clinical Virology,** 123, 2020, 104232.

187. J. J. Voermans, D.G. Mulders, S.D. Pas, M.P. Koopmans, A.A. van der Eijk & R. Molenkamp, *Performance Evaluation of the Panther Fusion® Respiratory Tract Panel*, **Journal of Clinical Virology,** 123, 2021, 104232.

188. M.J. Loeffelholz & Y.W. Tang, *Laboratory Diagnosis of Emerging Human Coronavirus Infections–The State of the Art,* **Emerging microbes & infections,** 9(1), 2020, 747-756.

189. J. A. Garson, S. Badru, E. Parker, R. S. Tedder, & M.O. McClure, *Highly Sensitive and Specific Detection of the SARS-CoV-2 Delta Variant by Double-Mismatch Allele-Specific Real Time Reverse Transcription PCR*, **Journal of Clinical Virology,** 146, 2022, 105049.

190. B.R.P. Lopes, G.S. da Silva, G. de Lima Menezes, J. de Oliveira, A.S.A. Watanabe, B. N. Porto & K.A. Toledo, *Serine Proteases in Neutrophil Extracellular Traps Exhibit Anti-Respiratory Syncytial Virus Activity,* **International Immunopharmacology,** *106*, 2022, 108573.

191. J.A. Garson, S. Badru, E.L. Parker, R.S. Tedder, & M.O. McClure, *Highly Sensitive and Specific Detection of the SARS-CoV-2 Delta Variant by Double-Mismatch Allele-Specific PCR*, **Medrxiv,** 2, 2021, 10.

192. M. Galloux, N. Gsponer, V. Gaillard, B. Fenner, T. Larcher, M. Vilotte & O. Nyanguile, *Targeting the Respiratory Syncytial Virus N0-P Complex with Constrained A-Helical Peptides in Cells and Mice,* **Antimicrobial Agents and Chemotherapy,** 64(10), 2020, 00717-20.

193. E.A. Van Erp, A.J. Lakerveld, E. de Graaf, M.D. Larsen, R.M. Schepp, A.L. Hipgrave Ederveen & P.B. van Kasteren, *Natural Killer Cell Activation by Respiratory Syncytial Virus-Specific Antibodies is Decreased in Infants with Severe Respiratory Infections and Correlates with Fc-Glycosylation,* **Clinical & Translational Immunology**, 9(2), 2020, 1112.

194. S. P. Andeweg, R.M. Schepp, J. van de Kassteele, L. Mollema, G.A. Berbers & M. van Boven, *Population-Based Serology Reveals Risk Factors for RSV Infection in Children Younger than 5 Years,* **Scientific Reports,** 11(1), 2021, 1-8.

195. X. Yu, A.J. Lakerveld, S. Imholz, M. Hendriks, S.C. Ten Brink, H.L. Mulder & P.B. van Kasteren, *Antibody and Local Cytokine Response to Respiratory Syncytial Virus Infection in Community-Dwelling Older Adult,* **Msphere,** 5(5), 2020, 00577-20.

196. B.V. Ribeiro, T.A.R. Cordeiro, G.R.O. e Freitas, L.F. Ferreira & D.L. Franco. *Biosensors for the Detection of Respiratory Viruses: A Review,* **Talanta Open,** 2, 2020, 100007.

197. A. Kutsaya, T. Teros-Jaakkola, L. Kakkola, L. Toivonen, V. Peltola, M. Waris & I. Julkunen, *Prospective Clinical and Serological Follow-up in Early Childhood Reveals a High Rate of Subclinical RSV Infection and a Relatively High Reinfection Rate within the First 3 Years of Life,* **Epidemiology & Infection,** 144(8), 2021, 1622-1633.

198. K. Borochova, K. Niespodziana, K. Stenberg Hammar, M. van Hage, G. Hedlin, C. Söderhäll & R. Valenta, *Features of the Human Antibody response against the Respiratory Syncytial Virus Surface Glycoprotein G,* **Vaccines,** 8(2), 2020, 337.

199. K.A. Swanson, J.N. Rainho-Tomko, Z.P. Williams, L. Lanza, M. Peredelchuk, M. Kishko & G. J. Nabel, *A Respiratory Syncytial Virus (RSV) F Protein Nanoparticle Vaccine Focuses Antibody Responses to a Conserved Neutralization Domain,* **Science Immunology,** *5*(47), 2020, 6466.

200. E. A. van Erp, A. J. Lakerveld, E. de Graaf, M.D. Larsen, R.M. Schepp, A.L.H. Ederveen & P.B. van Kasteren, *NK Cell Activation by RSV-Specific Antibodies is decreased in Infants with Severe Respiratory Infections and Correlates with Fc-Glycosylation*, **Clin Transl Immunol,** *9*, 2020, 1112.

201. W. Fonseca, C.A. Malinczak, C.F. Schuler, S.K. Best, A.J. Rasky, S.B. Morris & N. W. Lukacs, *Uric Acid Pathway Activation during Respiratory Virus Infection Promotes Th2 Immune Response via Innate Cytokine Production and ILC2 Accumulation*, **Mucosal immunology,** *13*(4), 2020, 691-701.

202. F. Pecora, F. Persico, A. Argentiero, C. Neglia, & S. Esposito, *The Role of Micronutrients in support of the Immune Response against Viral Infections,* **Nutrients,** *12*(10), 2020, 3198.

203. D. Laubreton, C. Drajac, J.F. Eléouët, M.A. Rameix-Welti, R. Lo-Man, S. Riffault, & D. Descamps, *Regulatory B Lymphocytes Colonize the Respiratory Tract of Neonatal Mice and Modulate Immune Responses of Alveolar Macrophages to RSV Infection in IL-10-Dependant Manner*, **Viruses,** 12(8), 2020, 822.

204. J. Stambas, C. Lu, & R. A. Tripp, *Innate and Adaptive Immune Responses in Respiratory Virus Infection: Implications for the Clinic*, **Expert Review of Respiratory Medicine,** 14(11), 2020, 1141-1147.

205. C.A. Malinczak, N.W. Lukacs & W. Fonseca, *Early-life Respiratory Syncytial Virus Infection, Trained Immunity and Subsequent Pulmonary Diseases,* **Viruses**, *12*(5), 2020, 505.

206. R. Ortiz Moyano, F. Raya Tonetti, M. Tomokiyo, P. Kanmani, M. G. H. Vizoso-Pinto, Kim & J. Villena, *The Ability of Respiratory Commensal Bacteria to beneficially modulate the Lung Innate Immune response is a Strain Dependent Characteristic,* **Microorganisms,** *8*(5), 2020, 727.

207. J. Anderson, L. A. H. Do, D. Wurzel, Z. Q. Toh, K. Mulholland, D. G. Pellicci & P. V. Licciardi, *Severe Respiratory Syncytial Virus Disease in Preterm Infants: A Case of Innate Immaturity*, **Thorax,** 76(9), 2021, 942-950.

208. S. Esposito, B. Abu Raya, E. Baraldi, K. Flanagan, F. Martinon Torres, M. Tsolia & S. Zielen. *RSV Prevention in All Infants: which is the most Preferable Strategy?* **Frontiers in Immunology,** 13, 2022, 880368.

209. K.M. Eichinger, J.L. Kosanovich, M. Lipp, K.M. Empey & N. Petrovsky, Strategies *for Active and Passive Pediatric RSV Immunization,* **Therapeutic Advances in Vaccines and Immunotherapy,** 9, 2021, 2515135520981516.

210. D. Tokuhara, & N. Hikita, *Cord Blood-Based Approach to Assess Candidate Vaccine Adjuvants Designed for Neonates and Infants,* **Vaccines,** 9(2), 2021, 95.

211. E.R. Shaw & H.C. Su, *The Influence of Immune Immaturity on Outcome after Virus Infections,* **The Journal of Allergy and Clinical Immunology: In Practice,** *9*(2), 2021, 641-650.

212. D. Wilkins, Y. Yuan, Y. Chang, A.A. Aksyuk, B.S. Núñez, U. Wählby-Hamrén & M. T. Esser, *Durability of Neutralizing RSV Antibodies following Nirsevimab Administration and Elicitation of the Natural Immune Response to RSV Infection in Infants*, **Nature Medicine**, 2, 2023, 1-8.

213. J. Anderson, C. M. Thang, L. Q. Thanh, V. T. T. Dai, V. T. Phan, B. T. H. Nhu & P. V. Licciardi, *Immune Profiling of Cord Blood from Preterm and Term Infants reveals Distinct differences in Pro-Inflammatory responses,* **Frontiers in Immunology,** 12, 2021, 777927.

214. H. C. Bergeron & R. A. Tripp, *Immunopathology of RSV: An Updated Review.* **Viruses,** 13(12), 2021, 2478.

215 I.R. Glowinski, A. Mejias & O. Ramilo, *New Preventive Strategies for Respiratory Syncytial Virus Infection in Children.* **Current Opinion in Virology,** 51, 2021, 216-223.

216. G. Di Mattia, R. Nenna, E. Mancino, V. Rizzo, A. Pierangeli, A. Villani & F. Midulla. *During the COVID-19 Pandemic where has Respiratory Syncytial Virus gone?* **Pediatric Pulmonology,** 56(10), 2021, 3106-3109.

217. H. Brenes-Chacon, C. Garcia-Mauriño, M. Moore-Clingenpeel, S. Mertz, F. Ye, D. M. Cohen & A. Mejias, *Age-Dependent Interactions among Clinical Characteristics, Viral Loads, and Disease Severity in Young Children with Respiratory Syncytial Virus Infection*, **The Pediatric Infectious Disease Journal,** 40(2), 2021, 116.

218. T. Démoulins, M. Brügger, B. Zumkehr, B.I. Oliveira Esteves, K. Mehinagic, A. Fahmi & M. P. Alves, *The Specific Features of the Developing T Cell Compartment of the Neonatal Lung are a Determinant of Respiratory Syncytial Virus Immunopathogenesis*, **PLoS Pathogens,** 17(4), 2021, 1009529.

219. J. B. Domachowske, E.J. Anderson & M. Goldstein, *The Future of Respiratory Syncytial Virus Disease Prevention and Treatment,* **Infectious Diseases and Therapy,** *10*, 2021, 47-60.

220. D. XZ, S. Song, X.Q. Qin, Y. Xiang, X.P. Qu, H.J. Liu, & C. Liu, *Research Progress of Respiratory Syncytial Virus (RSV) Infection and Respiratory Diseases in Infancy*, **Sheng Li Xue Bao:[Acta Physiologica Sinica],** *73*(6), 2021, 1043-1053.

221. G. A. Rossi, S. Ballarini, M. Silvestri, O. Sacco & A. A. Colin, *Respiratory Syncytial Virus* and *Airway Microbiota–A Complex Interplay* and *Its Reflection* on *Morbidity*, **Pediatric Allergy and Immunology,** 32(6), 2021, 1141-1151.

222. A.K. Simon, G.A. Hollander & A. McMichael, *Evolution of the Immune system In Humans from Infancy to Old Age,* **Proceedings of the Royal Society B: Biological Sciences,** 282(1821), 2019, 20143085.

223. D. Tokuhara & N. Hikita, *Cord Blood-Based Approach to Assess Candidate Vaccine Adjuvants Designed for Neonates and Infants,* **Vaccines**, 9, 2021, 95.

224. J.J. Carvajal, A.M. Avellaneda, C. Salazar-Ardiles, J. E. Maya, A.M. Kalergis & M. K. Lay*, Host Components Contributing to Respiratory Syncytial Virus Pathogenesis,* ***Frontiers in Immunology*****,** *10*, 2019, 2152.

225. D. Verhoeven, *Influence of Immunological Maturity on Respiratory Syncytial Virus-Induced Morbidity in Young Children*, **Viral Immunology,** 32(2), 2019, 76-83.

226. X. Wen, S. Mo, S. Chen, G. Yu, L. Gao, S. Chen & E. Liu, *Pathogenic difference of Respiratory Syncytial Virus Infection in Cotton Rats of Different Ages,* **Microbial Pathogenesis,** *137*, 2019, 103749.

227. A.N. Munteanu, M. Surcel, R.I. Huică, G. Isvoranu, C. Constantin, I.R. Pîrvu & M. Neagu, *Peripheral Immune Cell Markers in Children with Recurrent Respiratory Infections in the Absence of Primary Immunodeficiency,* **Experimental and Therapeutic Medicine,** 18(3), 2019, 1693-1700.

228. B.S. Graham, *Immunological Goals for Respiratory Syncytial Virus Vaccine Development*, **Current Opinion in Immunology,** 59, 2019, 57-64.

229. P. Li, Y. Zhang, W. Shen, S. Shi, & Z. Zhao, DbGSRV: *A Manually Curated Database of Genetic Susceptibility to Respiratory Virus,* **Plos One,** 17(3), 2022, 0262373.

230. T.H. Mogensen, *Genetic Susceptibility to Viral Disease in Humans*. **Clinical Microbiology and Infection**, 2, 2022, 1-2.

231 F. Darbeheshti, M. Mahdiannasser, B.D. Uhal, S. Ogino, S. Gupta & N. Rezaei. *Interindividual Immunogenic Variants: Susceptibility to Coronavirus, Respiratory Syncytial Virus and Influenza Virus,* **Reviews in Medical Virology,** 31(6), 2021, 2234.

232. H. O. IG Giamberardino, A.P. Pacheco, L.A. Pereira, M.D.C. Debur, G. Genehold & S.M. Raboni, *Respiratory Syncytial Virus, Host Genetic Susceptibility and Factors Associated with Disease Severity in a Cohort of Pediatric Patients*, **Journal of Tropical Pediatrics,** *68*(6), 2022, 091.

232. E. Ohashi, I. Hayakawa, Y. Murofushi, M. Kawai, S. Suzuki-Muromoto, Y. Abe & M. Kubota, *Recurrent Acute Necrotizing Encephalopathy in a Boy with RANBP2 Mutation and Thermolabile CPT2 Variant, The first case of ANE1 in Japan*, **Brain and Development,** *43*(8), 2021 873-878.

234. B. Puthothu, M. Krueger, J. Heinze, J. Forster, & A. Heinzmann, *Impact of IL8 and IL8-Receptor Alpha Polymorphisms on the Genetics of Bronchial Asthma and Severe RSV Infections*, **Clinical and Molecular Allergy**, 4, 2022**,** 1-6.

235. C. Azzari, E. Baraldi, P. Bonanni, E. Bozzola, A. Coscia, M. Lanari, & F. Mosca, *Epidemiology and Prevention of Respiratory Syncytial Virus Infections in Children in Italy*, **Italian Journal of Pediatrics,** 47, 2021, 1-12.

236. J. B. Domachowske, E. J. Anderson & M. Goldstein, *The Future of Respiratory Syncytial Virus Disease Prevention and Treatment*, **Infectious Diseases and Therapy,** 10, 2021, 47-60.

237. Wikipedia, 2023, "Respiratory Syncytial Virus", *Wikimedia Foundation, Last modified October 14, 2023.* https://en.wikipedia.org/wiki/Respiratory_syncytial_virus

238. J. Smith, P. Petrovic, M. Rose, C. De Souz, L. Muller, B. Nowak & J Martinez, *Placeholder Text: A Study*, **The Journal of Citation Styles**, 2, 2021, *3.* https://doi.org/10.10/X

239. C. Griffiths, S.J. Drews, & D. J. Marchant. *Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment,* **Clinical Microbiology Reviews**, *30*(1), 2017, 277–319. https://doi.org/*10.1128/CMR.00010-16*

240. A. Jha, H. Jarvis, C. Fraser, & P. J. Openshaw, *Respiratory Syncytial Virus, In SARS, MERS and other Viral Lung Infections, Available at:* 2016. http://www.ncbi.nlm.nih.gov/pubmed/20399493

241. J. A. Coultas, R. Smyth & P. J. Openshaw, *Respiratory Syncytial Virus (RSV): A Scourge from Infancy to Old Age,* **Thorax**, 74(10), 2019, 986–993. https://doi.org/10.1136/thoraxjnl-2018-212212

242. A. R. Falsey, & E.E. Walsh, *Respiratory Syncytial Virus Infection in Adults,* **Clinical Microbiology Reviews**, 13(3), 2000, 371–384. https://doi.org/10.1128/CMR.13.3.371

243. T.N. Cressey, S.L. Noton, K. Nagendra, M.R. Braun, R. Fearns, *Mechanism for de novo Initiation at Two Sites in the Respiratory Syncytial Virus Promoter,* **Nucleic Acids Res**, 46(13), 2018, 6785-6796.

244. V. M. Cowton, D. R. McGivern, *Unravelling the complexities of respiratory syncytial virus RNA synthesis*, **Journal of General Virology**, 87(7), 2006, 1805–1821. https://doi.org/10.1099/vir.0.81786-0

245. C. E. Jeffree, H. W. M. Rixon, G. Brown, J. Aitken & R. J. Sugrue, *Distribution of the Attachment (G) Glycoprotein and GM1 within the Envelope of Mature Respiratory Syncytial Virus Filaments Revealed Using Field Emission Scanning Electron Microscopy*, **Virology**, 306(2), 2003, 254–267. https://doi.org/10.1016/S0042-6822(02)00016-8

246. S. F. Ausar, M. Espina, J. Brock, N. Thyagarayapuran, R. Repetto, L. Khandke & C. R. Middaugh, *High-Throughput Screening of Stabilizers for Respiratory Syncytial Virus: Identification of Stabilizers and Their Effects on the Conformational Thermostability of Viral Particles*, **Human Vaccines**, 3(3), 2007, 94–103. https://doi.org/10.4161/hv.3.3.4149

247. P. Sastre, A. G. P. Oomens, & G. W. Wertz, *The Stability of Human Respiratory Syncytial Virus is enhanced by Incorporation of the Baculovirus GP64 Protein*. **Vaccine**, 25(27), 2007, 5025–5033. https://doi.org/10.1016/j.vaccine.2007.04.066

248. J. Rawling, O. Cano, D. Garcin, D. Kolakofsky, &J. A. Melero, *Recombinant Sendai Viruses Expressing Fusion Proteins with Two Furin Cleavage Sites Mimic the Syncytial and Receptor-Independent Infection Properties of Respiratory Syncytial Virus*, **Journal of Virology**, *85*(6), 2011, 2771–2780. https://doi.org/10.1128/JVI.02065-10

249. P. L. Collins, R. Fearns, &B. S. Graham. *Respiratory Syncytial Virus: Virology, Reverse Genetics, and Pathogenesis of Disease*. **Current Topics in Microbiology and Immunology**, 372, 2013, 3–38. https://doi.org/10.1007/978-3-642-38919-1_1

250. S. Techaarpornkul, N. Barretto, M.E. Peeples, *Functional Analysis of Recombinant Respiratory Syncytial Virus Deletion Mutants Lacking the Small Hydrophobic and/or Attachment Glycoprotein Gene,* **J Virol**, 75(15), 2001, 6825-6834.

251. R. Malhotra, M. Ward, H. Bright, R. Priest, R. Foster Martyn, M. Hurle, E. Blair, M. Bird, *Isolation and Characterisation of Potential Respiratory Syncytial Virus Receptor(s) on Epithelial Cells,* **Microbes Infect**, 2003, 5(2), 123-133.

252. H. San-Juan-Vergara, V. Sampayo-Escobar, N. Reyes, B. Cha, L. Pacheco-Lugo, T. Wong, M.E. Peeples, P.L. Collins, M.E. Castaño, S.S. Mohapatra, *Cholesterol-Rich Micro Domains as Docking Platforms for Respiratory Syncytial Virus in Normal Human Bronchial Epithelial Cells,* **J Virol,** 2012, 86(3), 1832-1843.

253. T. King, A. Mejias, O. Ramilo, M.E. Peeples, *The Larger Attachment Glycoprotein of Respiratory Syncytial Virus produced in Primary Human Bronchial Epithelial Cultures Reduces Infectivity for Cell Lines,* **PLoS Pathog**, 17(4), 2021, 1009469.

254. L.K. Hallak, D. Spillmann, P.L. Collins, M.E. Peeples, *Glycosaminoglycan Sulfation Requirements for Respiratory Syncytial Virus Infection*, **J. Virol**, 74(22), 2000, 10508-10513.

255. S.M. Johnson, B.A. McNally, I. Ioannidis, E. Flano, M.N. Teng, A.G. Oomens, E.E. Walsh, M.E. Peeples, *Respiratory Syncytial Virus Uses CX3CR1 as a Receptor on Primary Human Airway Epithelial Cultures*, **PLoS Pathog**, 11(12), 2015, 1005318.

256. M. Molteni, S. Gemma, C Rossetti, *The Role of Toll-Like Receptor 4 in Infectious and Noninfectious Inflammation*, **Mediators Inflamm**, 2, 2016, 6978936.

257. E.A. Kurt-Jones, L Popova, L Kwinn, L.M. Haynes, L.P. Jones, R.A. Tripp, E.E. Walsh, M.W. Freeman, D.T. Golenbock, L.J. Anderson, R.W. Finberg, *Pattern Recognition Receptors TLR4 and CD14 Mediate Response to Respiratory Syncytial Virus,* **Nature Immunology**,1(5), 2000, 398-401.

258. A.K. Behera, H. Matsuse, M. Kumar, X. Kong, R.F. Lockey, S.S. Mohapatra, *Blocking Intercellular Adhesion Molecule-1 on Human Epithelial Cells Decreases Respiratory Syncytial Virus Infection*, **Biochem Biophys Res Commun** 280(1), 2001, 188-195.

259. M.G. Currier, S. Lee, C.C. Stobart, A.L. Hotard, R. Villenave, J. Meng, C.D. Pretto, M.D. Shields, M.T. Nguyen, S.O. Todd, M.H. Chi, J. Hammonds, S.A. Krumm, P. Spearman, R.K. Plemper, K. Sakamoto, R.S. Jr Peebles, U.F. Power, M.L. Moore, *EGFR Interacts with the Fusion Protein of Respiratory Syncytial Virus Strain 2-20 and Mediates Infection and Mucin Expression*, **PLoS Pathog**, 12(5), 2016, 005622.

260. F. Tayyari, D. Marchant, T.J. Moraes, W. Duan, P. Mastrangelo, R.G. Hegele, *Identification of Nucleolin as a Cellular Receptor for Human Respiratory Syncytial Virus,* **Nat Med**, 17(9), 2011, 1132-1135.

261. S. Nisole, E.A. Said, C. Mische, M.C. Prevost, B. Krust, P. Bouvet, A. Bianco, J.P. Briand, A.G. Hovanessian, *The Anti-HIV Pentameric Pseudopeptide HB-19 Binds the C-Terminal End of Nucleolin and Prevents Anchorage of Virus Particles in the Plasma Membrane of Target Cells,* **The Journal of Biological Chemistry**, 277(23), 2002 20877-20886

262. S. Bose, M. Basu, A.K. Banerjee, *Role of Nucleolin in Human Parainfluenza Virus Type 3 Infection of Human Lung Epithelial Cells,* **J Virol,** 78(15), 2004, 8146-8158

263. P.Y. Su, Y.F. Wang, S.W. Huang, Y.C. Lo, Y.H. Wang, S.R. Wu, D.B. Shieh, S.H. Chen, J.R. Wang, M.D. Lai, C.F. Chang, *Cell Surface Nucleolin Facilitates Enterovirus 71 Binding and Infection,* **J Virol,** 89(8), 2015, 4527-4538.

264. J-T. Lee, L-Y. Chang, L-C. Wang, C-L. Kao, P-L. Shao, C-Y. Lu, P-I. Lee, J-M. Chen, C-Y. Lee, L-M. Huang, *Epidemiology of Respiratory Syncytial Virus Infection in Northern Taiwan, 2001-2005 — Seasonality, Clinical Characteristics, and Disease Burden,* **J Microbiol Immunol Infect,** 40, 2007, 293-301.

265. J. Zhu, Q. Miao, J. Tang, X. Wang, D. Dong, T. Liu, R. Qi, Z. Yang, G. Liu, *Nucleolin Mediates the Internalization of Rabbit Hemorrhagic Disease Virus through Clathrin-Dependent Endocytosis*, **PLoS Pathog,** 14(10), 2018, 1007383.

266. C.D. Griffiths, L.M. Bilawchuk, J.E. McDonough, K.C. Jamieson, F. Elawar, Y. Cen, W. Duan, C. Lin, H. Song, J-L. Casanova, S. Ogg, L.D. Jensen, B. Thienpont, A. Kumar, T.C. Hobman, D. Proud, T.J. Moraes, D.J. Marchant, *IGF1R is An Entry Receptor for Respiratory Syncytial Virus*, **Nature**, 583(7817), 2020, 615-619.

267. M. Lingemann, T. McCarty, X. Liu, U.J. Buchholz, S. Surman, S.E. Martin, P.L. Collins, S. Munir, *The Alpha-1 subunit of the Na+,K+-ATPase (ATP1A1) is required*

for Macropinocytic Entry of Respiratory Syncytial Virus (RSV) in Human Respiratory Epithelial Cells, **PLoS Pathog**, 15(8), 2019, 1007963.

268. H. San-Juan-Vergara, V. Sampayo-Escobar, N. Reyes, B. Cha, L. Pacheco-Lugo, T. Wong, M.E. Peeples, P.L. Collins, M.E. Castaño, S.S. Mohapatra, *Cholesterol-rich Microdomains as Docking Platforms for Respiratory Syncytial Virus in Normal Human Bronchial Epithelial Cells*, **J Virol**, 86(3), 2012, 1832-1843.
269. M.A. Krzyzaniak, M.T. Zumstein, J.A. Gerez, P. Picotti, A. Helenius, *Host Cell Entry of Respiratory Syncytial Virus involves Macropinocytosis followed by Proteolytic Activation of the F Protein***, PLoS Pathog,** 9(4), 2013, 1003309.

270. P. L. Collins & B. S. Graham, *Viral and Host Factors in Human Respiratory Syncytial Virus Pathogenesis*, **Journal of Virology**, *82(5),* 2008*, 2040–2055.* https://doi.org/10.1128/JVI.01625-07

271. A.C. Nascimento-Carvalho, O. Ruuskanen, & C. M. Nascimento-Carvalho, *Comparison of the Frequency of Bacterial and Viral Infections Among Children with Community-acquired Pneumonia Hospitalized Across Distinct Severity Categories*: *A Prospective Cross-Sectional Study*, **BMC Pediatrics**, 2, 16(1), 2016. https://doi.org/10.1186/S12887-016-0645-3

272. C. B. Wonodi, M. Deloria-Knoll, D. R. Feikin, A. N. DeLuca, A. J. Driscoll, J. C. Moïsi, H. L. Johnson, D. R. Murdoch, K. L. O'Brien, O. S. Levine, & J. A. G. Scott, *Evaluation of Risk Factors for Severe Pneumonia in Children: The Pneumonia Etiology Research for Child Health Study*, **Clinical Infectious Diseases,** 54(2), 2012, 124–131. https://doi.org/10.1093/cid/cir1067

273. R. J. Pickles, & J. P. DeVincenzo, *Respiratory Syncytial Virus (RSV) and Its Propensity for causing Bronchiolitis,* **The Journal of Pathology,** *235*(2), 2015, 266–276. https://doi.org/10.1002/PATH.4462

274. P. Mastrangelo, M. J. Norris, W. Duan, E. G. Barrett, T. J. Moraes, & R. G. Hegele *Targeting Host Cell Surface Nucleolin for RSV Therapy: Challenges and Opportunities*. **Vaccines**, 5(3), 2017, 2. https://doi.org/10.3390/VACCINES5030027

275. X. Yuan, T. Hu, H. He, H. Qiu, X. Wu, J. Chen, M. Wang, C. Chen, & S. Huang, *Respiratory Syncytial Virus Prolifically Infects N2a Neuronal Cells, Leading to TLR4 and Nucleolin Protein Modulations and RSV F Protein Co-Localization with TLR4 and Nucleolin*, **Journal of Biomedical Science,** *25*(1), 2018, 1. https://doi.org/10.1186/S12929-018-0416-6

276. G. Piedimonte, & M. K. Perez, *Respiratory Syncytial Virus Infection and Bronchiolitis Pediatrics in Review,* 35(12), 2014, 519–530. https://doi.org/10.1542/PIR.35-12-519

277. B. D. Persson, A. B, R. Fearns & H. Danahay, *Respiratory Syncytial Virus can Infect Basal Cells and Alter Human Airway Epithelial Differentiation,* **PLoS ONE**, 9(7), 2014, 2. https://doi.org/10.1371/JOURNAL.PONE.0102368

278. L. Liu, S. Oza, D. Hogan, J. Perin, I. Rudan, J. E. Lawn, S. Cousens, C. Mathers, & R. E. Black, *Global, Regional, and National causes of Child Mortality in 2000-13,*

with Projections to Inform Post-2015 Priorities: An Updated Systematic Analysis, **The Lancet**, 385(9966), 2013, 430–440. https://doi.org/10.1016/S0140-6736(14)61698-6.

279. R. C. Welliver, P. A. Checchia, J. H. Bauman, A. W. Fernandes, P. J. Mahadevia & C. B. Hall. *Fatality Rates in Published Reports of RSV Hospitalizations among High-Risk and Otherwise Healthy Children*, **Current Medical Research and Opinion**, 26(9) 2010, 2175–2181. https://doi.org/10.1185/03007995.2010.505126

280. R. Villenave, S. Thavagnanam, S. Sarlang, J. Parker, I. Douglas, G. Skibinski, L. G. Heaney, J. P. McKaigue, P. V. Coyle, M. D. Shields, & U. F. Power, *In Vitro Modeling of Respiratory Syncytial Virus Infection of Pediatric Bronchial Epithelium, The Primary Target of Infection in Vivo*, *Proceedings of the National Academy of Sciences of the United States of America*, *109*(13), 2012, 5040–5045. https://doi.org/10.1073/PNAS.1110203109

281. M. K. Lay, P. A. González, M. A. León, P. F. Céspedes, S. M. Bueno, C. A. Riedel, & A. M. Kalergis, *Advances in Understanding Respiratory Syncytial Virus Infection in Airway Epithelial Cells and Consequential Effects on the Immune Response, Microbes and Infection,* 15(3), 2013, 230–242. https://doi.org/10.1016/J.MICINF.2012.11.012

282. R. M. Liesman, U. J. Buchholz, C. L. Luongo, L. Yang, A. D. Proia, J. P. DeVincenzo, P. L. Collins, & R. J. Pickles, *RSV-encoded NS2 Promotes Epithelial Cell Shedding and Distal Airway Obstruction,* **Journal of Clinical Investigation**, 124(5), 2014, 2219–2233. https://doi.org/10.1172/JCI72948

283. R. Fearns, *The Respiratory Syncytial Virus Polymerase: A Multitasking Machine, Trends Microbiol*, 27(12), 2019, 969-971.

284. T. P. Welliver, R. P. Garofalo, Y. Hosakote, K. H. Hintz, L. Avendano, K. Sanchez, L. Velozo, H. Jafri, S. Chavez-Bueno, P. L. Ogra, L. A. McKinne, J. L. Reed & R. C. Welliver, *Severe Human Lower Respiratory Tract Illness caused by Respiratory Syncytial Virus and Influenza Virus is characterized by the Absence of Pulmonary Cytotoxic Lymphocyte Responses,* **Journal of Infectious Diseases**, 195(8), 2007, 1126–1136. https://doi.org/10.1086/512615

285. M. L. García-García, C. Calvo, A. Moreira, J. A. Cañas, F. Pozo, B. Sastre, S. Quevedo, I. Casas, & V. Del Pozo, *Thymic Stromal Lymphopoietin, IL-33, and Periostin in Hospitalized Infants with Viral Bronchiolitis,* **Medicine (United States)**, 96(18), 2017, 2-3. https://doi.org/10.1097/MD.0000000000006787

286. M. A. Gill, K. Long, T. Kwon, L. Muniz, A. Mejias, J. Roy, L. Connolly, J. Banchereau & O. Ramilo, *Differential Recruitment of Dendritic Cells and Monocytes to Respiratory Mucosal Sites in Children with Influenza Virus or Respiratory Syncytial Virus Infection*, **Journal of Infectious Diseases,** *198*(11), 2008, 1667–1676. https://doi.org/10.1086/593018

287. J. Saravia, D. You, B. Shrestha, S. Jaligama, D. Siefker, G.I. Lee, J.N. Harding, T.L. Jones, C. Rovnaghi, B. Bagga, J.P. DeVincenzo, S.A. Cormier, *Respiratory Syncytial Virus Disease Is Mediated by Age-Variable IL-33*, **PLoS Pathog,** 11(10), 2015, 1005217.

288. K. Rayavara, A. Kurosky, S. J. Stafford, N. J. Garg, A. R. Brasier, R. P. Garofalo, & Y. M. Hosakote, *Proinflammatory Effects of Respiratory Syncytial Virus–Induced Epithelial HMGB1 on Human Innate Immune Cell Activation*, **The Journal of Immunology**, 201(9), 2018, 2753–2766. https://doi.org/10.4049/JIMMUNOL.1800558

289. J. Han, A. Dakhama, Y. Jia, M. Wang, W. Zeng, K. Takeda,, Y. Shiraishi, M. Okamoto, S. F. Ziegler, & E. W. Gelfand, *Responsiveness to Respiratory Syncytial Virus in Neonates is Mediated Through Thymic Stromal Lymphopoietin and OX40 Ligand*, **Journal of Allergy and Clinical Immunology,** 130(5), 2012, 2. https://doi.org/10.1016/J.JACI.2012.08.033

290. H. C. Lee, M. B. Headley, Y. M. Loo, A. Berlin, M. Gale, J. S. Debley, N. W. Lukacs, & S. F. Ziegler, *Thymic Stromal Lymphopoietin is induced by Respiratory Syncytial Virus-Infected Airway Epithelial Cells and Promotes a Type 2 Response to Infection,* **Journal of Allergy and Clinical Immunology,** 130(5), 2012, 3. https://doi.org/10.1016/J.JACI.2012.07.031

291. R. Dey, M.A. Folkins, N.J. Ashbolt, *Extracellular Amoebal-Vesicles: Potential Transmission Vehicles for Respiratory Viruses*, **npj Biofilms and Microbiomes**. 7(1), 2021, 25.

292. M. Hu, K.E. Schulze, R. Ghildyal, D.C. Henstridge, J.L. Kolanowski, E.J. New, Y. Hong, A.C, P.M. Hansbro, P.A. Wark, M.A. Bogoyevitch, D.A. Jans, *Respiratory Syncytial Virus Co-Opt,* Hsu *s Host Mitochondrial Function to Favour Infectious Virus Production*, **Elife,** (8), 2019, 3.

293. D.R. Morris, Y. Qu, A. Agrawal, R.P. Garofalo, A. Casola, *HIF-1α Modulates Core Metabolism and Virus Replication in Primary Airway Epithelial Cells Infected with Respiratory Syncytial Virus*, **Viruses**, 12(10), 2020, 2.

294. A. Kalinowski, B.T. Galen, I.F. Ueki, Y. Sun, A. Mulenos, A. Osafo-Addo, B. Clark, J. Joerns, W. Liu, J.A. Nadel, C.S. Dela Cruz, J.L. Koff, *Respiratory Syncytial Virus Activates Epidermal Growth Factor Receptor to Suppress Interferon Regulatory Factor 1-Dependent Interferon-Lambda and Antiviral Defense in Airway Epithelium,* **Mucosal Immunol**, 11(3), 2018, 958-967.

295. J. Qiao, A. Li, & X Jin, TSLP from RSV-Stimulated Rat Airway Epithelial Cells Activates Myeloid Dendritic Cells, *Immunology and Cell Biology*, *89*(2), 2011, 231–238. https://doi.org/10.1038/ICB.2010.85

Chapter Three

Methodology

3.1 Study Site

The study took place at the Biorepository Clinical Virology Laboratory (BVCL) at the University College Hospital, (UCH) Ibadan. The site was selected to be used for convenience and because the samples used were well collected and properly stored.

3.2 Sample Design

The study is a retrospective cross sectional survey design. Age, sex and local Government was obtained from the clinical records of selected participants.

3.3 Sample Participant

Stored samples of children aged 5 and below that tested negative for Covid-19 and older adults' samples 15-83 years who also tested negative for Covid -19 were used for the experiment.

3.4 Sample Size

Sample size was calculated using the Leslie Kish formula for single proportions.

$N = Z^2pq/d^2$

Sample size= Z^2pq/d^2

Z= Standardized normal deviation which is always a constant (1.96) at 95% confidence interval

Strains =85.7% =0.857% (Faneye 2004)

Q =1-p (1-0.857) (0.143)/0.05^2

N= $\underline{Z^2pq}$ = $\underline{1.96^2 \text{ X } 0.857 \text{ X } 0.143}$ = 188.32 approx. 188 with addition of 20% =206

d^2 0.05^2

The number of samples used for the analysis were 206.

3.5. Sample Collection

Archived samples stored frozen in -80^0c ultralow freezer (Nasopharyngeal and Oropharyngeal) swab were obtained by gentle rubbing the deep nasal turbing bilaterally with sterile cotton wool and from the posterior pharynx combined collected for COVID-19 at the Biorepository Clinical Virology Laboratory (BCVL) was analyzed in the study.

3.6 Laboratory Procedures

Viral RNA was extracted directly from the samples using RNA easy Mini Viral RNA kit (Qiagen). The samples were allowed to thaw at room temperature in a biosafety cabinet observing the PPE, i.e. using lab coat, personnel slippers and gloves.5.6microlitre of carrier RNA was added to 560 microliters of AVL buffer

560µl of prepared buffer AVL containing carrier RNA was pippeted into a 1.8ml Eppendorf tube.140µl of samples was added to the buffer AVL-carrier RNA in the Eppendorf tube. Pulse voltexing was done for 15s to ensure the sample lysis efficiently and the sample mixed thoroughly with buffer AVL to get homogenous solution.

The mixture was incubated at room temperature for 10mins after which it was centrifuged to remove drops from the inside of the lid. 560µl of ethanol (96%-100%) was added to the

sample, and mixed by pulse vortexing for 15s, and also centrifuged for the same reason mentioned earlier.

Exactly 560ul of the solution (Lysate) was carefully applied to the QI Amp Mini column (in a 2ml collection tube) without wetting the rim. The cap was closed, and centrifuged at 8000rpm for 1min. The QIA amp, mini column was placed into a clean 2ml collection tube and the tube containing the filtrate discarded.

In continuation, 500µl of buffer AW1 was added to the QIAamp Mini column, and centrifuged at 12,000rpm for 1min to remove lysed cell wall from the solution. Waste liquid was discarded and binding column placed back in another collection tube. 500µl of buffer AW2 was added to the tube and centrifuged at 12000rpm for 3mins, the QLA amp Mini column was then placed in a clean 2ml collection tube and centrifuge at a full speed for 1min to dry the membrane completely.

The QI amp Mini column was placed in a new 1.5ml micro centrifuge tube, 60µl of buffer AVE was added and incubated at 800rpm for 1minute. The extracted viral RNA was used for reverse transcription and PCR Amplification. All the remaining RNA was stored at -20^{o}c for further use.

Real time PCR was carried out on the extracted RNA with the aid of Allplex fluorescence PCR detection technology already designed by the manucfacturer using a standard procedure with specific primers and probes for influenza A virus, Influenza B virus and Respiratory Syncytial Virus respectively, so as to realize their rapid detection in the samples to be tested. The Allplex Fluorescence kit was purchased from the Guangdong Huayin Medicine Science Co, Ltd. Third floor zone, Guangdong science and technology innovation Base, 80 Lanyue Road, Science Park High and new Tech. Development District, 510663 Guangdong province; PEOPLE, s REPULBLIC OF CHINA FluA/Flu B/RSV RT-PCR Master Mix contains target

gene primers, Probes, reaction buffer, dNTPs, Mg2+, Taq Enzyme, reverse transcriptase, in a lyophilized powder x1 bottle.

The FluA/FluB/RSV positive control contains inactivated virus culture in a lyophilizedx1tube the procedures will be carried out on ice.

The FluA/FluB/RSV Negative control will contain physiological saline in a 0.25ml x1tube

Redissolved diluent containing purified water in 1.40ml x 1tube

3.7 Reaction Preparation

The master mix was opened according to the arrow direction of the aluminum, plastic cover, 1ml of Redissolved diluent was added, strongly mixed on the vortex for more than one minute and allow to stand for 30-60seconds until the liquid was clear and transparent. It was sub packaged into PCR reaction tubes according to 20ul tubes.

Samples to be tested, InfA/InfB/RSV negative control was extracted simultaneously. The positive control was Redissolved with 250ul of redissolved diluent and mixed well before use.20ul of the redissolved RT-PCR master mix was added into each PCR reaction tube,5ul of extracted samples including positive and negative controls was also added into each corresponding PCR reaction tubes. After adding the samples, the PCR reaction tubes were centrifuged for 15s on a palm centrifuge and then deliver to the nucleic acid amplification region. If bubbles were found the tube wall were gently flicked to remove it and centrifuged again. The FluA/FluB/RSV positive control contains inactivated virus culture in a lyophilizedx1tube the procedures was carried out on ice.

The FluA/FluB/RSV Negative control contain physiological saline in a 0.25ml bottle

Table 3.1: Recommended Setting of Reaction Procedure

Steps	Temperature(°c)	Time	Cycle
1. Reverse transcription	50	10 min	1
2. Pre-denaturation	95	2min	1
3. Denaturation	95	5s	45
4. Annealing, extension and fluorescence collection	60	35s	45
5. Result analysis			

Source: Author's Field Work, 2023

The primers and probe was designed by the manufacturer of the kit following a standard procedure.

Primer or probe	Oligonucleotide sequence, 51-31	Target gene or region
InfA		
Forward primer	CAA GAC CAA TCY TGT CAC CTC	
Reverse primer	GCA TTY TGG ACA AAV CGT CTA CG	
Probe	TGC AGT CCT /ZEN/CGC TCA CTG GGC ACG	Matrix protein
InfB		
Forward primer	TCC TCA AYT CAC TCT TCG AGC AGC G	Nonstructural protein
Reverse primer	CGG TGC TCT TGA CCA AAT TGG	
Probes	CCA ATT CGA /ZEN/GCA GCT GAA ACT GCG GTG	nonstructural Protein
RSV-A (N gene)		
Forward A21	5! GCTCTTAGGAAAGTCAAGTTGAA	
Reverse A102	5! TGCTCCGTTGGATGGTGTATT	
Probe APB48	5! ACACTCAACAAAGATCAACTTCTGTCATCCAGC	
(N gene) RSV-B		
Forward B17	5! GATGGCTCTTAGCAAAGTCAAGTTAA	
Reverse B120	5! TGTCAATATTAT GCCTGTACTACGTTGAA	
Probe BPB45	5! TGATACATTAAATAAGGATCAGCTGCTGTCATCCA	

The published sequence of the N-gene for the RSV A2 Strain (Genbank assession number M111486

3.8 Ethical Consideration

Ethical approval was obtained from the UI/UCH Research Ethics Committee UCH Ibadan and Oyo State Ethics Committee Secretariat Ibadan. The information obtained was confidentially handled by giving unique identifiers to each study participants. The identifiers will be used e.g. AD001 for the first participant in adult while CH001 for the first participant of children and subsequently like that. The identifiers will be used to analyze the data obtained. Result template will be pass worded or kept from unauthorized access to the research records

3.9 Data Management

Data obtained was processed and analyzed using statistical packages SPSS version 25. Result was presented using descriptive statistics like means and percentages.

Endnotes

1. A. Faneye, O.M. Babatunde, A. Adesanmi, B. Onoja, *Evaluation of IgG Antibodies Against Respiratory Syncitial Virus RSV and Associated risk Factors for Severe Repistory Tract Infection in Pre-School Children in North-Central Nigeria,* **African Journal Infect Dis,** 8(2), 2014, 36-39.

2. B.O. Shu, K. Marie, W. Kirby, W.G. Davis, C. Warnes, J. Liau, J.M. Winchell, *Multiplex Real-Time Reverse Transcription PCR for Influenza A Virus, Influenza B Virus, and Severe Acute Respiratory Syndrome Corona Virus*, **Journal of Emerging Infectious Diseases,** 27(7), 2021, 3. https ;//doi.org/10.3201/eid2707.2104612.

Chapter Four

Results and Discussion of Findings

4.1 Results of Findings

4.2 Distribution of RSV, Influenza A and Influenza B among Children by Sociodemographic Characteristics

The sociodemographic characteristics of the study population are highlighted in Table 4.4. The study encompassed a diverse group of 106 participants, spanning an age range of 1 to 5 years. The mean age ± SD was 2.97 ± 1.620. None of the Infections considered was statistically significant in the age groups considered as the P-value was greater than 0.05.

45.3% of children were male and 54.7% were female. All occurrence of Influenza B infection was found among children (n=3). RSV occurred more in female children than in male children. There was no statistically significant association between gender and outcome of infection of RSV and Influenza B.

Location of study participants was grouped by senatorial districts: Oyo North (Kajola, Iwajowa), Oyo Central (Egbeda, Lagelu, Oluyole, Akinyele) and Oyo South (Ibadan S/West, Ibadan S/East, Ibadan North, Ibadan N/East, Ido). Majority of the participants were from Oyo Central with 67.9%. All instances of prevalence of Influenza B and RSV occurred in Oyo Central. There was no statistically significant association between location and outcome of infection of RSV and Influenza B.

Feature	Years	No. Participants n (%)	INF. A Positive Participants n (%)	INF. B Positive Participants n (%)	RSV Positive Participants N (%)
	5 years	33 (31.4)	0	1 (3.0)	1 (3.0)
Age	4 years	6 (5.7)	0	0	0
	3 years	21 (20.0)	0	1 (4.8)	0
	2 years	15 (14.3)	0	0	1 (6.7)
	1 year	30 (28.6)	0	1 (3.3)	1 (3.3)
	p-value			**0.916**	**0.827**

Table 4.1: Prevalence of Infection Across Sociodemographic Groups

Source: Author's Field Work, 2023

Table 4.2: Prevalence of Infection Across Gender in Children

Feature	Gender	No. Participants n (%)	INF. A Positive Participants n (%)	INF. B Positive participants n (%)	RSV Positive Participants N (%)
Sex	Male	58 (45.3)	0	3 (100)	1(33.3)
	Female	48 (54.7)	0	0	2(66.7)
p-value				**0.250**	**0.589**

Source: Author's Field Work, 2023

Table 4.3: Prevalence of Infection Across Oyo State in Study Participating Children

Location	Senatorial District	No. Participants n (%)	INF. A Positive Participants n (%)	INF. B Positive participants n (%)	RSV Positive Participants N (%)
	Oyo North	2 (1.9)	0	0	
	Oyo Central	72 (67.9)	0	3 (100)	3 (100)
	Oyo South	32 (30.2)	0	0	0
p-value				**0.482**	**0.482**

Source: Author's Field Work, 2023

4.3 Overall Prevalence of RSV, Influenza A and Influenza B among children

The molecular analysis of samples revealed that 2.8% (n = 3) of the study participants were infected with Influenza B. Likewise, 2. 8% of participants were infected with RSV. There was no infected participant for Influenza A. Data is presented on Table 4.4.

Table 4.4: Prevalence of Infection Among Children

	Positive n (%)	Negative n (%)	Total
Inf. A	**0**	**106(100)**	**106**
Inf. B	**3 (2.8)**	**103 (97.2)**	**106**
RSV	**3 (2.8)**	**103 (97.2)**	**106**

Source: Author's Field Work, 2023

4.4 Distribution of RSV, Influenza A and Influenza B Among Adults by Sociodemographic Characteristics

The sociodemographic characteristics of the study population are highlighted in Table 4.3. Some of the participants did not supply their sociodemographic information. Such participants were grouped as 'undisclosed' during statistical analysis.

The study encompassed a diverse group of 100 participants, span**ning an age range of 15 to 83 years. The mean age ± SD was 33.50±14.022. Majority of the participants were between** 15 **to 35 years old (49.0).** None of Infections considered was statistically significant in the age groups considered as the P-value was greater than 0.05.

55.0% of adult participants were male with 40.0 being female. All instances of Influenza B and RSV infection were found among adults who did not disclose their gender. There was statistically significant association between gender and outcome of infection of Influenza B and RSV infection

Location of study participants was grouped by senatorial districts. Oyo North (Atigbo), Oyo Central (Egbeda, Lagelu, Oluyole, Ona ara) and Oyo South (Ibadan North, Ibarapa, Ido). Majority of the participants were from Oyo South with 52.0%. All instances of Influenza infection occurred in Oyo Central, while that of Influenza A occurred in Oyo South. There was a statistically significant association between location and outcome of RSV infection with 0.049 P-value.

4.5 Prevalence of Infection Among Adults by Sociodemographic Characteristics

Characteristics	Age Range	No. Participans n (%)	INF. A Positive Participants n (%)	INF. B Positive Participants n (%)	RSV Positive Participants N (%)
Age	15-35	49 (49)	0	1(2.0)	1(2.0)
	36-50	25 (25)	1(100)	0	0
	≥51	10 (10)	0	0	0
	Undisclosed	16 (16)	0	0	1(50)
	p-value		0.387	0.789	0.534
	Mean Age				
	33.5±14.022				

Source: Author's Field Work, 2023

Table 4.6: Prevalence of Infection Across Gender (Adults)

		No. Participants n (%)	INF. A Positive Participants n (%)	INF. B Positive Participants n (%)	RSV Positive Participants N (%)
Gender	Male	55 (55.0)	1 (100)	0	0
	Female	40 (40.0)	0	0	0
	Undisclosed	5 (5.0)	0	1 (100)	2(100)
p-value			**0.662**	**0.000**	**0.000**

Source: Author's Field Work, 2023

Table 4.7: Prevalence of Infection across Locations/ Senatorial District (Adults)

Location		No. Participants n (%)	INF. A Positive Participants n (%)	INF. B Positive Participants n (%)	RSV Positive Participants N (%)
	Oyo North	5 (5.0)	0	0	0
Oyo State	Oyo Central	37 (37.0)	0	1(100)	1(50)
	Oyo South	52 (52.0)	1(100)	0	0
	Undisclosed	6 (6.0)	0	0	1(50)
	p-value		0.818	0.633	0.049

Source: Author's Field Work, 2023

4.5 Overall Prevalence of RSV, Influenza A and Influenza B Among Adults

The molecular analysis of samples revealed that 1.0% (n=1) of the study participants were infected with Influenza A. Likewise, 1.0% (n=1) of participants were infected with Influenza B. RSV reported 2.0% prevalence (n=2). Data is presented on Table 4.8.

Table 4.8: Prevalence of Infection Among Adults

	Positive	Negative	Total
Inf. A	1 (1.0)	99 (99.0)	100
Inf. B	1 (1.0)	99 (99.0)	100
RSV	2 (2.0)	98 (98.0)	100

Source: Author's Field Work, 2023

4.6 Discussion of Findings

The study involved 106 children, of whom three (3) were positive for RSV, while two (2) were positive for influenza B and none were positive for influenza A. Of the 100 adults, two (2) were positive for RSV and one (1) was positive for influenza A. In a bigger study in the US on Global burden of respiratory infections associated with seasonal influenza in children under 5 years found a 10.1 million influenza virus-associated Acute Lower Respiratory Infection (ALRI) cases (68151); 870,000 influenza virus-associated ALRI hospitalizations (5430001415000), 15300 in-hospital deaths (580043800), and a total of up to 34800 (1320097200) influenza virus-associated ALRI deaths. Influenza virus was responsible for 7% of ALRI cases, 5% of ALRI hospitalizations, and 4% of ALRI deaths in children younger than 5 years. However, this much bigger study did not address Adults[1].

The mean age of children in the study was 2.97years ± 1.620 and RSV prevalence of 2.8%. Mean age of older adults was 33.50 years ±14.022 and RSV prevalence of 2.0%. In a closer geographical location study by Faneye, 2004, a prevalence rate of 85.7% was recorded in the tested children and 23.3% in the control children across all age groups and genders. A statistically significant difference in age groups was found in patients with LRTI ($p < 0.05$), age < 1 41%, age 1 < 5 27.6%[2].

A total of 45.3% of children were male and 54.7% were female. Strikingly, our study showed a decline in the prevalence rate of RSV. This may significantly be due to the vaccine coverage of the geographical location (Oyo State) in which this present study was carried out, unlike the North-Central Nigeria where another study was carried out in their study, showing a location, still experiencing the challenge to push up vaccine coverage. There was no significant association between gender and infections with RSV (P-value 0.589) and influenza B (p-value 0.250) both ≥ 0.05. Approximately, 55.0% of adults were male and

40.0% female ,5% did not disclose their gender (Table 4.6) There was significant association between gender and outcome of influenza B and RSV infection in adults (p-value ,0.000 ≤ 0.005) (Table 4.1.3.1). There remains a dearth of information with regards to the prevalence of Influenza A&B in Nigeria going by the records of NCDC, 2023. However, another study showed, that adult females are more likely to develop severe influenza disease than the male[3]. Exactly, 52.0% of the total participants were from Oyo South while 37% from Oyo central and 5% from Oyo North, 6% did not disclose their location (Table 4.7). The prevalence of Influenza B and RSV in Oyo Central was 37% while that of Influenza A in Oyo South was 52% and RSV 6% among undisclosed (Table4.1.3.2). There was no significant association between location and outcome of infection of RSV, and Influenza B (p value was 0.482.) (Table 4.3)

Prevalence of RSV was 2.8%, influenza A was 0% and B was 2.8% in children while in older adults, RSV prevalence was 2.0%; Influenza A was 1.0%, and B was 1% (Table 4.4) and (Table 4.8)

Respiratory viruses share common symptoms like coughing, sneezing fever etc. thus it is important to do a proper diagnosis during the period of covid-19 as to be able to know the type of treatment to commence.

None of the infection was statistically significant in the age groups, 45.3% of the children were male while 54.7% were female, all occurrence of influenza was found among children n=3.RSV occurred more in female than male children. No statistically significant association between gender and outcome of infection of RSV and influenza B

The location of the participant was grouped according to senatorial district; majority of the participants were from Oyo Central with 87.9%. All instances of prevalence of influenza B and RSV occurred in Oyo Central. There was no statistically significant association between location or outcome of RSV and influenza B.

The molecular analysis revealed overall prevalence of RSV, influenza A and Influenza B among children to be 2.8%, (n=3) were infected with influenza. Likewise, 2.0% were infected with RSV. No infected participant with influenza A. In contrast, previous sentinel studies conducted from 1999 to 2018 in the United States of RSV and influenza-related deaths showed a higher RSV prevalence rate of 19.6% and influenza A of about 63%, however, this study did not address influenza B.[4] Notably, their study observed the highest RSV-related mortality in children under one year of age and those over 65 years of age. Our study was conducted in Oyo State, southwestern Nigeria, a sub-Saharan region of known tolerance to respiratory diseases, in contrast to the temperate zone (USA), where respiratory diseases are a major challenge.

Endnotes

1. X. Wang, L. You, K. Brien, P. Byasi, S.B. Omah, D. Abass, A. Ali, E. Azziz, *Global Burden of Respiratory Infections Associated with Seasonal Influenza in Chidren Under 5 Yaers in 2018: A Systematic Review and Modelling Study*, **Lancent Global Health**, 8(4), 2020, 497-510, Doi: 10.1016/S2214-109X (19)30545-5.

2. O Faneye, M Babatunde, B. Onoja, A. Adesanmi, *Evaluation of IgG antibodies against Respiratory Syncitial Virus RSV and Associated Risk Factors for Severe Repistory Tract Infection in Pre-School Children in North-Central Nigeria*, **African Jounal of Infectious Disease**, 8(2), 2014, 36-39

3. M. Rosemary, S.L. Klein, *The Interception of Sex and Gender in the Treatment of Influenza*; curr, **Opin Virol**, (35), 2019, 35-41 doi: 10.1016/**J. Coviro**.2019.04.009.

4. C. Chelsea, C. Dehlinger, C. Nypayer, *Influenza and Influenza Vaccine: A Review*; **J, Midwifery Womens Health**, 66(1), 2021, 45-53.

Chapter Five

Conclusion

5.1 Summary of Findings

This study makes use of secondary data which were stored samples originally collected from adults older and 5 years children and below that show symptoms of Covid-19 but were tested negative. To establish the main objective of this study, the prevalence of other respiratory viruses was determined. Because 5 years children and below are more prone to the respiratory infections especially RSV, 106 children samples were used for the analysis,3 were positive for RSV, while 2 were positive for Influenza B, while there are no positive for influenza A. Also,100 adult samples were used for the analysis because older adults too are prone, two were positive for RSV while one was positive for influenza A which were our targeted genes according to the kit that was used for the analysis.

Respiratory viruses share common symptoms like coughing, sneezing fever etc. thus it is important to do a proper diagnosis during the period of COVID-19 as to be able to know the type of treatment to commence.

This study made use of the new technique for investigation. Real time PCR was done using the AllPLEX kit to detect the presence of RSV, Influenza A and Influenza B in the samples used.

206 samples were used for this study, the male to female ratio is about 1to1, female 52.8%, and male 47.2%. Molecular analysis shows that 1.0% were infected with influenza A likewise 1% were also infected with influenza B, RSV reported 2.0%, prevalence

The study encompassed a diverse group of 106 children participant spanning age 1-5years, mean age SD =2.97. None of the infection was statistically significant in the age groups 45.3% of the children were male while 54.7% were female, all occurrence of influenza was

found among children n=3.RSV occurred more in female than male children. No statistically significant association between gender and outcome of infection of RSV and influenza B.

The location of the participant was grouped according to senatorial district; majority of the participants were from Oyo Central with 87.9%. All instances of prevalence of influenza B and RSV occurred in Oyo Central. There was no statistically significant association between location or outcome of RSV and influenza B.

The molecular analysis revealed overall prevalence of RSV, influenza A and Influenza B among children to be 2.8%, n=3 were infected with influenza Likewise 2.0% were infected with RSV. No infected participant with influenza A.

Some of the adult do not supply their Sociodemographic information, the adult participant used spanning ages 15-83 years. The mean age is 33.5%, majority were within 15-35years, and it is not statistically significant.55% were male while 40% were female. Influenza B and RSV were found among those that do not declare their age.

There is co-infection between Covid-19, RSV and Influenza A and Influenza B. This shows that there is a good relationship between the means of the disease development among the respiratory viruses. Being a new study, the observations obtained from this can also be extended to other viruses by examining the coinfections.

5.2 Conclusion

This study shows that after covid-19 have been ruled out from the sample, other respiratory infection like RSV and influenza A and B can also present same symptoms like Covid-19 thus there is need for a proper diagnosis to ascertain the exacting virus bringing similar symptoms of RSV. This studies shows that some children did not complete their immunization i.e. those positive for influenza B. The research is also valid because we found the gene of interest in some of the samples amplified, i.e influenza B and RSV. There is need

to screen for other influenza viruses in Negative samples of Covid and during pandemic not to make Covid the only target RSV is not a challenge; it will only take time for the immunocompressed people to heal if diagnosed on time. Adult too can come down with influenza. Among the positive people for RSV, further studies should be carried to check the following; Do they have underlining sickness, are they immunocompressed,

5.3 Recommendations

As revealed by this study there is need for every laboratory to: -

(1) Get a more sensitive testing kit like the one used in this study so that different viruses present in a sample

(2) There is need for effective preventive measures like good hygiene practices like washing of hands and not touching of surfaces anyhow.

(3) The use of effective infection prevention and control measures in health facilities i.e. use of personal protective equipment (PPE)

(4) Effort should be made to increase awareness of RSV among healthcare providers

(5) Awareness to be created for policy makers and general public to facilitate early diagnosis of RSV as a coinfection in respiratory diseases.

(6) Adequate funding and investment in research is needed for RSV diagnosis.

(7) Efforts should be made to increase easy access to effective vaccines and treatment in other to reduce the prevalence.

(8) Efforts should be made to reduce the staying of children 5 years and below in daycare centers during the cold season.

(9) Children should be vaccinated for influenza virus.

(10) Efforts should be made for a support regiment for adults especially the elderly if no detected on time so that they can overcome it on time instead of the system to be fighting it which may not be easy and fast because of their immune which is or may be very low

5.4 Contribution to Knowledge

This study shows that there are many infections having similar symptoms thus they must be well isolated for proper diagnosis and treatment. It enables policy makers to be aware of the infection called Respiratory Syncytial virus and will make prevention and treatment with other coinfection be effective. It will make the whole public to also be aware of the infection and be intentional in the prevention.

5.5 Suggested Area for Further Research

There is need for further studies on this work by having relationship with the positive people for RSV and influenza A and B virus to know if they are immunosuppressed people by collecting their blood samples for a full blood count, and also check their diet if they are not eating good food, life style and also see I they are low class people, the elderly to see if they are diabetics patient

Relationship of RSV with other respiratory viruses like rhinovirus, enterovirus (like polio or picorna virus) Sars, parainfluenza and the remaining influenza viruses; Influenza C and

Bibliography

Journals

Al-Hanawi M. K, Angawi K, Alshareef N, Qattan A, Kattan W. M, & Alsharqi O, *Knowledge, Attitude and Practice Toward COVID-19 Among the Public in the Kingdom of Saudi Arabia: A Cross-Sectional Study,* **Frontiers in Public Health,** 8, 2020, 217.

Alshaghdali K., Saeed M, Kamal M. A, &Saeed A, *Interaction of Ectodomain of Respiratory Syncytial Virus G Protein with TLR2/TLR6 Heterodimer: An in Vitro and in Silico Approach to Decipher the Role of RSV G Protein in Pro-Inflammatory Response Against the Virus,* **Current Pharmaceutical Design,** 27(44), 2021, 4464-4476.

Amoo A., *Respiratory Syncytial Virus Infection Among Children in Lagos, Nigeria*, ***J Clin Immunol Microbiol*****,** 2(1), 2021, 1-11.

Ahmed S, Khudair M. K, & Ahmed T, *Study Role of Respiratory Syncytial Virus Associated with Infection of Respiratory System of Children in AL-Miqdadiya/Diyala,* **Indian Journal of Forensic Medicine & Toxicology,** 15(3), 2021, 5519.

Alvares P. A, *SARS-CoV-2 and Respiratory Syncytial Virus Coinfection in Hospitalized Pediatric Patients*, **The Pediatric Infectious Disease Journal,** 40(4), 2021, 164-166.

Arriola C., S, Kim L, Langley G, Anderson E. J, Openo K, Martin A. M, & Chaves S. S, *Estimated Burden of Community-Onset Respiratory Syncytial Virus–Associated Hospitalizations Among Children Aged< 2 years in the United States,* 2014–15, **Journal of the Pediatric Infectious Diseases Society,** 9(5), 2020, 587-595.

Azzari, C., Baraldi, E, Bonanni, Bozzola P, Coscia E, A Lanari M & Mosca, F, *Epidemiology and Prevention of Respiratory Syncytial Virus Infections in Children in Italy*, **Italian Journal of Pediatrics**, 47, 2021, 1-12.

Anderson J, Thang C. M, Thanh L. Q, Dai V. T. T, Phan V. T, Nhu B. T. H, & Licciardi P. V, *Immune Profiling of Cord Blood from Preterm and Term Infants Reveals Distinct Differences in Pro-Inflammatory Responses,* **Frontiers in Immunology,** *12,* 2021, 777927.

Andeweg S.P, Schepp R.M, Van De Kassteele J, Mollema L, Berbers G. A, & Van Boven M, *Population-Based Serology Reveals Risk Factors for RSV Infection in Children Younger than 5 years*, ***Scientific Reports*****,** *11*(1) 2021, 1-8.

Ausar, S. F, Espina M, Brock J, Thyagarayapuran N, Repetto R, Khandke L, & Middaugh, C. R, *High-Throughput Screening of Stabilizers for Respiratory Syncytial Virus: Identification of Stabilizers and their Effects on the Conformational Thermostability of Viral Particles*, **Human Vaccines**, 3(3), 2007, *94–103.* https://doi.org/10.4161/hv.3.3.4149

Ayouni I, Maatoug J, Dhouib W, Zammit N, Fredj S. B, & Ghannem H, *Effective Public Health Measures to Mitigate the Spread of COVID-19: A Systematic Review,* **BMC Public Health,** 21 2021, 1015.

Azene Z. N, Merid M. W, Muluneh A. G, Geberu D. M, Kassa G. M, & Yenit M. K, *Adherence Towards COVID-19 Mitigation Measures and its Associated Factors Among Gondar City Residents: A Community-Based Cross-Sectional Study in Northwest Ethiopia*, **PLoS ONE** 15(12) 2020, 33378332.

Bai Y, Yao L, Wei T, Tian F, Jin D.Y, Chen L, & Wang M, *Presumed Asymptomatic Carrier Transmission of COVID-19*, **Jama,** 323(14), 2020, 1406-1407.

Barbati F, Moriondo M, Pisano L, Calistri E, Lodi L, Ricci S, & Azzari C, *Epidemiology of Respiratory Syncytial Virus-Related Hospitalization over a 5-year Period in Italy: Evaluation of Seasonality and Age Distribution before Vaccine Introduction*, **Vaccines**, *8*(1), 2020, 15.

Bardsley M, Morbey R A, Hughes H. E, Beck C. R, Watson C. H, Zhao H, & Elliot A. J, *Epidemiology of Respiratory Syncytial Virus in Children Younger than 5 years in England During the COVID-19 Pandemic, Measured by Laboratory, Clinical, and Syndromic Surveillance: a Retrospective Observational Study*, **The Lancet Infectious Diseases,** *23*(1), 2023, 56-66.

Bayomi R, *Effect of Teaching Guidelines on Knowledge, Attitudes, and Practices Regarding COVID 19 Among the First Year Nursing Students*, **Assiut Scientific Nursing Journal,** 9(25), 2021, 38-47.

Behera A. K, Matsuse H, Kumar M, Kong X, Lockey R. F, Mohapatra S. S, *Blocking Intercellular Adhesion Molecule-1 on Human Epithelial Cells Decreases Respiratory Syncytial Virus Infection*, **Biochem Biophys Res Commun**, 280(1), 2001, 188-195.

Belser J. A, & Tumpey T. M, *The 1918 Flu, 100 years later,* **Science,** 359(6373), 2019, 255-255.

Bergeron H. C, & Tripp R. A, *Immunopathology of RSV: an Updated Review*, **Viruses,** 13(12), 2021, 2478.

Bianchini S, Silvestri E, Argentiero A, Fainardi V, Pisi G, & Esposito S, *Role of Respiratory Syncytial Virus in Pediatric Pneumonia*, **Microorganisms,** 8(12), 2020, 2048.

Billard M. N, Van De B. P. M, L. Ven, Baraldi, L Kragten-Tabatabaie, J, Bont, & J. G. Wildenbeest, *International Changes in Respiratory Syncytial Virus (RSV) Epidemiology During the COVID-19 Pandemic: Association with School Closures,* **Influenza and Other Respiratory Viruses**, 16(5), 2022, 926-936.

Boehm A.B, Hughes B, Duong D, Chan-Herur V, Buchman A, Wolfe M. K, & White B. J, *Wastewater Surveillance of Human Influenza, Metapneumovirus, Parainfluenza, Respiratory Syncytial Virus (RSV), Rhinovirus, and Seasonal Coronaviruses During the COVID-19 Pandemic,* **Medrxiv**, 20, 2022, 9.

Bohmwald K, Gálvez N. M, Canedo-Marroquín G, Pizarro-Ortega M.S, Andrade-Parra C, *Gómez-Santander F, & Kalergis A. M., Contribution of Cytokines to Tissue Damage During Human Respiratory Syncytial Virus Infection*, **Frontiers in Immunology,** 10, 2019, 452.

Borochova K, Niespodziana K, Stenberg Hammar K, Van Hage M, Hedlin G, Söderhäll C, & Valenta R, *Features of the Human Antibody Response Against the Respiratory Syncytial Virus Surface Glycoprotein G,* **Vaccines,** *8*(2), 2020, 337.

B. O Shu, K. Kirby, G. William *et al*; *Multiplex Real-Time Reverse Transcription PCR for Influe nza A Virus, Influenza B Virus, and Severe Acute Respiratory Syndrome Corona Virus*, https ;//doi.org/10.3201/eid2707.2104612.

Branche A. R, Saiman L, Walsh E. E, A. R., Falsey A. R, Sieling W. D, Greendyke W, & Finelli L, *Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017–2020,* **Clinical Infectious Diseases,** 74(6), 2022, 1004-1011.

Brooks S. K, Webster R. K, Smith L. E, Woodland L, Wessely S, & Rubin G. J, *The Psychological Impact of Quarantine and How to Reduce it: Rapid Review of the Evidence*, **The Lancet**, 395(10227), 2020, 912-920.

Bose S, Basu M, Banerjee A.K, *Role of Nucleolin in Human Parainfluenza Virus Type 3 Infection of Human Lung Epithelial Cells,* **J Virol**, 78(15), 2004, 8146-8158.

Buendía J. A, & Patiño D. G, *Costs of Respiratory Syncytial Virus Hospitalizations in Colombia*, **PharmacoEconomics-Open**, 5, 2021, 71-76.

Brenes-Chacon H, Garcia-Mauriño C, Moore-Clingenpeel M, Mertz S, Ye F, Cohen D. M, & Mejias A, *Age-Dependent Interactions Among Clinical Characteristics, Viral Loads, and Disease Severity in Young Children with Respiratory Syncytial Virus Infection*, **The Pediatric Infectious Disease Journal,** 40(2), 2021, 116.

Cowton, V. M., McGivern, D. R., & Fearns, R. (2006), *Unravelling the Complexities of Respiratory Syncytial Virus RNA Synthesis*, **Journal of General Virology**, 87(7), 1805–1821. https://doi.org/10.1099/vir.0.81786-0

Cruz J. S, De Souza Luna L. K, Alves V. R. G, Conte D. D, & Bellei N. C. J, *Viral Load of Respiratory Syncytial Virus Among Children from Primary Care and Hospital Settings Admitted to a University Hospital in Brazil (2009-2013)*, **Journal of Medical Virology,** *93*(6), 2021, 3397-3400.

Cantú-Flores K, Rivera-Alfaro G, Muñoz-Escalante J. C, & Noyola D. E, Global Distribution of Respiratory Syncytial Virus A and B Infections: a Systematic Review, **Pathogens and Global Health,** 116(7), 2022, 398-409.

Carvajal J. J, Avellaneda A. M, Salazar-Ardiles C, Maya J. E, Kalergis A. M, & Lay M. K, *Host Components Contributing to Respiratory Syncytial Virus Pathogenesis*, **Frontiers in Immunology,** 10, 2019, 2152.

Casalegno J. S, Ploin D, Cantais A, Masson E, Bard E, Valette M, & Gillet Y, *Characteristics of the Delayed Respiratory Syncytial Virus Epidemic, 2020/2021*, Rhône Loire, France, ***Eurosurveillance*****,** 26(29), 2021, 2100630.

Chatterjee A, Mavunda K, & Krilov L. R, *Current State of Respiratory Syncytial Virus Disease and Management*, **Infectious Diseases and Therapy,** 10, 2021, 5-16.

Chelsea C, Dehlinger C, Nypayer C, *Influenza and Influenza Vaccine: A Review*; J **Midwifery Womens Health** 66(1), 2021, 45-53.

Choi E. J, Wu W, Cong X, Zhang K, Luo, Ye S, & Bao X, *Broad Impact of Exchange Protein Directly Activated by cAMP 2 (EPAC2) on Respiratory Viral Infections*, **Viruses,** *13*(6), 2021, 1179.

Chung H. Y, Jian M J, Chang C. K, Lin J C, Yeh K. M, Chen C. W, & Shang H. S, *Novel Dual Multiplex Real-Time RT-PCR Assays for the Rapid Detection of SARS-CoV-2, Influenza A/B, and Respiratory Syncytial Virus Using the BD MAX Open System,* **Emerging Microbes & Infections**, *10*(1), 2021, 161-166.

Chwartz D. A, & Dhaliwal A, *Infections in pregnancy with COVID-19 and other respiratory RNA virus diseases are rarely, if ever, transmitted to the fetus: experiences with coronaviruses, parainfluenza, metapneumovirus respiratory syncytial virus, and influenza,* **Archives of Pathology & Laboratory Medicine**, 144(8), 2020, 920-928.

Clifford S, McNab L. A, Ha Do V, Crawford N. W, Daley A, Mulholland K, & Wurzel D, *Changing Epidemiology of Respiratory Syncytial Virus in Australia—Delayed Re-Emergence in Victoria Compared to Western Australia/New South Wales (WA/NSW) After Prolonged Lock-Down for CoronaVirus Disease 2019 (COVID-19),* **Clinical Infectious Diseases,** *73*(12), 2021, 2365-2366.

Collins P. L, & Graham B. S, *Viral and Host Factors in Human Respiratory Syncytial Virus Pathogenesis*, **Journal of Virology**, 82(5), 2008, 2040–2055. https://doi.org/10.1128/JVI.01625-07

Collins P. L, Fearns R, & Graham B. S, *Respiratory Syncytial Virus: Virology, Reverse Genetics, and Pathogenesis of Disease***, Current Topics in Microbiology and Immunology**, 372, 2013, 3–38. https://doi.org/10.1007/978-3-642-38919-1_1

Corsello T, Qu Y, Ivanciuc T, Garofalo R. P, & Casola A, *Antiviral Activity of Extracellular Vesicles Derived from Respiratory Syncytial Virus-Infected Airway Epithelial Cells,* **Frontiers in Immunology**, 2, 2022, 13.

Coultas J. A, Smyth R, & Openshaw P. J, *Respiratory Syncytial Virus (RSV): a Scourge from Infancy to Old Age,* **Thorax**, 74(10), 2019, 986–993. https://doi.org/10.1136/thoraxjnl-2018-212212

Cressey T. N, Noton S. L, Nagendra K, Braun M. R, Fearns R, *Mechanism for De Novo Initiation at Two Sites in the Respiratory Syncytial Virus Promoter,* **Nucleic Acids Res**, 46(13), 2018, 6785-6796.

Currier M. G, Lee S, Stobart C. C, Hotard A. L, Villenave R, Meng J, Pretto C. D, Shields M. D, Nguyen M.T , Todd S. O, Chi M. H, Hammonds J, Krumm S. A, Spearman P, Plemper R. K, Sakamoto K, *Peebles RS Jr, Power UF, Moore ML. EGFR Interacts with the Fusion Protein of Respiratory Syncytial Virus Strain 2-20 and Mediates Infection and Mucin Expression*, **PLoS Pathog,** 12(5), 2016, 1005622**.**

D. A, Foley, D. K, Yeoh C. A, Minney-Smith A. C, Martin A. O, Mace, C. T, Sikazwe, & C. C. Blyth, *The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of CoronaVirus Disease 2019–Related Public Health Measures,* **Clinical Infectious Diseases,** 73(9), 2021, 2829-2830.

Darbeheshti F, Mahdiannasser M, Uhal B. D, Ogino S, Gupta S, & Rezaei N, I*nterindividual Immunogenic Variants: Susceptibility to CoronaVirus, Respiratory Syncytial Virus and Influenza Virus,* **Reviews in Medical Virology,** 31(6), 2021, 2234.

Debnath S. K, Debnath M, & Srivastava R, *Opportunistic Etiological Agents Causing Lung Infections: Emerging Need to Transform Lung-Targeted Delivery*, **Heliyon**, 2, 2022, 12620.

Demont C, Petrica N, Bardoulat I, Duret S, Watier L, Chosidow A, & Lemaitre M, *Economic and Disease Burden of RSV-Associated Hospitalizations in Young Children in France, from 2010 through 2018*, **BMC Infectious Diseases,** *21*(1), 2021, 730.

Démoulins T, Brügger M, Zumkehr B, Oliveira Esteves B. I, Mehinagic K, Fahmi A, & Alves M. P, *The Specific Features of the Developing T Cell Compartment of the Neonatal Lung are a Determinant of Respiratory Syncytial Virus Immunopathogenesis*, **PLoS Pathogens,** 17(4), 2021, 1009529.

Dey R, Folkins M. A, Ashbolt N. J, *Extracellular Amoebal-Vesicles: Potential Transmission Vehicles for Respiratory Viruses*, **npj Biofilms and Microbiomes**, 7(1), 2021, 25.

Di Mattia G, Nenna R, Mancino E, Rizzo V, Pierangeli A, Villani A, & Midulla F, *During the COVID-19 Pandemic Where has Respiratory Syncytial Virus Gone?*, **Pediatric Pulmonology**, 56(10), 2021, 3106-3109.

Dicker K, Järvelin A. I, Garcia-Moreno M, & Castello A, *The Importance of Virion-Incorporated Cellular RNA-Binding Proteins in Viral Particle Assembly and Infectivity,* **In Seminars in Cell & Developmental Biology**, 111, 2021, 108-118.

Dolnik O, Gerresheim G. K, & Biedenkopf N, *New Perspectives on the Biogenesis of Viral Inclusion Bodies in Negative-Sense RNA Virus Infections*, **Cells**, 10(6), 2021, 1460.

Domachowske J. B, Anderson E. J, & Goldstein M, *The Future of Respiratory Syncytial Virus Disease Prevention and Treatment,* **Infectious Diseases and Therapy**, 10, 2021, 47-60.

E. M, Earle's Minimum Essential Medium, & PBS, P. B. S, *Specimen Collection, Storage, and Transportation*, 2020.

Edwards K. M, *The Impact of Social Distancing for Severe Acute Respiratory Syndrome Coronavirus 2 on Respiratory Syncytial Virus and Influenza Burden,* **Clinical Infectious Diseases,** 72(12), 2021**,** 2076-2078.

Eichinger K. M, Kosanovich J. L, Lipp M, Empey K. M, & Petrovsky N, *Strategies for Active and Passive Pediatric RSV Immunization*, **Therapeutic Advances in Vaccines and Immunotherapy**, 9, 2021, 2515135520981516.

Esposito S, Abu Raya B, Baraldi E, Flanagan K, Martinon Torres F, Tsolia M, & Zielen S, *RSV Prevention in all Infants: Which is the Most Preferable Strategy,* **Frontiers in Immunology**, 13, 2022, 880368.

Eymieux S, Rouillé Y, Terrier O, Seron K, Blanchard E, Rosa-Calatrava M, & Roingeard P, *Ultrastructural Modifications Induced by SARS-CoV-2 in Vero Cells: a Kinetic Analysis of Viral Factory Formation, Viral Particle Morphogenesis and Virion Release,* **Cellular and Molecular Life Sciences**, 78, 2021, 3565-3576.

Falsey A. R, & Walsh E. E, *Respiratory Syncytial Virus Infection in Adults,* **Clinical Microbiology Reviews**, 13(3), 2000, 371–384. https://doi.org/10.1128/CMR.13.3.371

Faneye O, Babatunde M, Onoja B, *Evaluation of IgG Antibodies Against Respiratory Syncitial Virus RSV and Associated Risk Factors for Severe Repistory Tract Infection in Pre-School Children in North-Central Nigeria*, **African Journal of Infectious Disease**, 8(2), 2014, 36-39.

Fernandez-Sarmiento J, Corrales S. C, Obando E, Amin J, Goyes A. B, Lopez P. A. B, & Ortiz N.B, *Factors Associated with Severe Acute Respiratory Infections due to Rhinovirus/Enterovirus Complex in Children and their Comparison with those of Respiratory Syncytial Virus,* **Archives of Pediatric Infectious Diseases,** 10(2), 2022, 3.

Fearns R, *The Respiratory Syncytial Virus Polymerase: A Multitasking Machine,* **Trends Microbio**, 27(12), 2019, 2969-971

Fonseca W, Malinczak C.A, Schuler C.F, Best S. K, Rasky A. J, Morris S. B, & Lukacs N. W, *Uric Acid Pathway Activation during Respiratory Virus Infection Promotes Th2 Immune Response Via Innate Cytokine Production and ILC2 Accumulation*, **Mucosal Immunology,** 13(4), 2020, 691-701.

Franck K. T, Schneider U. V, Knudsen C, M, Ma, D, & Lisby G, *Evaluation of Immuview RSV Antigen Test (SSI Siagnostica) and BinaxNOW RSV Card (Alere) for Rapid Detection of Respiratory Syncytial Virus in Retrospectively and Prospectively Collected Respiratory Samples*, **Journal of Medical Virology,** *92*(12), 2020, 2992-2998.

Fourgeaud J, Toubiana J, Chappuy H, Delacourt C, Moulin F, Parize P, & Frange P, *Impact of Public Health Measures on the Post-COVID-19 Respiratory Syncytial Virus Epidemics in France*, **European Journal of Clinical Microbiology & Infectious Diseases**, 40, 2021, 2389-2395.

Garson J. A, Badru S, Parker E, Tedder R. S, & McClure M. O, *Highly Sensitive and Specific Detection of the SARS-CoV-2 Delta Variant by Double-Mismatch Allele-Specific Real Time Reverse Transcription PCR*, **Journal of Clinical Virology**, 146, 2022, 105049.

Grellet E, Goulet A, & Imbert I, *Replication of the Coronavirus Genome: A Paradox Among Positive Strand RNA Viruses*, **Journal of Biological Chemistry**, 298(5**)**, 2022, 101923.

Griffin M. P, Yuan Y, Takas T, Domachowske J. B, Madhi S. A, Manzoni P, & DeVincenzo J. P., *Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants*, **New England Journal of Medicine,** 383(5), 2020, 415-425.

Gill, M. A., Long, K., Kwon, T., Muniz, L., Mejias, A., Connolly, J., Roy, L., Banchereau, J., & Ramilo, O, *Differential Recruitment of Dendritic Cells and Monocytes to Respiratory Mucosal Sites in Children with Influenza Virus or Respiratory Syncytial Virus Infection.* **Journal of Infectious Diseases,** 198(11), 2008, 1667–1676. https://doi.org/10.1086/593018

Gualano M. R, Lo Moro G, Voglino G, Bert F, & Siliquini R, *Effects of COVID-19 Lockdown on Mental Health and Sleep Disturbances in Italy*, **International Journal of Environmental Research and Public Health**, 17(13), 2020, 4779.

Galloux M, Gsponer N, Gaillard V, Fenner B, Larcher T, Vilotte M, & Nyanguile O, *Targeting the Respiratory Syncytial Virus N0-P Complex with Constrained α-Helical Peptides in Cells and Mice,* **Antimicrobial Agents and Chemotherapy**, 64(10), 2020, 00717-20.

García-García M. L, Calvo C, Moreira A., Cañas J. A., Pozo F, Sastre B, Quevedo S, Casas I, & Del Pozo V, *Thymic Stromal lymphopoietin, IL-33, and Periostin in Hospitalized Infants with Viral Bronchiolitis,* **Medicine (United States)**, 96(18), 2017, 2. https://doi.org/10.1097/MD.0000000000006787

Gimferrer, Vila J, Piñana M, Andrés C, Rodrigo-Pendás J. A, Peremiquel-Trillas P, & Antón A, *Virological Surveillance of Human Respiratory Syncytial Virus A and B at a Ttertiary Hospital in Catalonia (Spain) During Five Consecutive Seasons*, **Future Microbiology**, 14(5), 2013-2018, 373-381.

Ginsburg A. S, & Srikantiah P, *Respiratory Syncytial Virus: Promising Progress Against a Leading Cause of Pneumonia,* **The Lancet Global Health,** 9(12), 2021, 1644-1645.

Glowinski R, Mejias A, & Ramilo O, *New Preventive Strategies for Respiratory Syncytial Virus Infection in Children*, **Current Opinion in Virology**, 51, 2021, 216-223.

Graham B. S, *Immunological Goals for Respiratory Syncytial Virus Vaccine Development,* **Current Opinion in Immunology,** 59, 2019, 57-64.

Griffiths C., Drews, S. J. & Marchant, D. J. (2017), *Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment,* **Clinical Microbiology Reviews**, 30(1), 277-319 https://doi.org/*10.1128/CMR.00010-16*

Griffiths C.D, Bilawchuk L.M, McDonough J.E, Jamieson K.C, Elawar F, Cen Y, Duan W, Lin C, Song H, Casanova J.L, Ogg S, Jensen L.D, Thienpont B, Kumar A, Hobman T.C, Proud D, Moraes T.J, Marchant D.J, *IGF1R is an Entry Receptor for Respiratory Syncytial Virus*, **Nature**, 583(7817), 2020, 615-619.

Groves H. E, Piché-Renaud P. P, Peci A, Farrar D. S, Buckrell S, Bancej C, & Morris S. K, *The Impact of the COVID-19 Pandemic on Influenza, Respiratory Syncytial Virus, and Other Seasonal Respiratory Virus Circulation in Canada: A Population-Based Study,* **The Lancet Regional Health-Americas,** 1, 2021, 100015.

Gupta N, & Ahmed S, Coronavirus: *An Overview of Genetics and Transmission Stages,* **Health Informatics and Technological Solutions for Coronavirus (COVID-19)**, 1, 2021, 41-63.

Haddadin Z, Beveridge S, Fernandez K, Rankin D. A, Probst V, Spieker A. J, & Halasa N, *Respiratory Syncytial Virus Disease Severity in Young Children*, **Clinical Infectious Diseases**, 73(11), 2021, 4384-4391.

Halabi K.C, Saiman L, & Zachariah P, The *Epidemiology of Respiratory Syncytial Cirus in New York City During the Coronavirus Disease-2019 Pandemic Compared with Previous Years*, **The Journal of Pediatrics**, 242, 2022, 242-244.

Hallak L.K, Spillmann D, Collins P.L, Peeples M.E, *Glycosaminoglycan Sulfation Requirements for Respiratory Syncytial Virus Infection*, **J. Virol**, 74(22), 2000,10508-10513

Han J, Dakhama A., Ji, Y, Wang M., Zeng W, Takeda K., Shiraishi Y, Okamoto, M., Ziegler, S. F., & Gelfand, E. W, *Responsiveness to Respiratory Syncytial Virus in Neonates is Mediated through Thymic Stromal Lymphopoietin and OX40 Ligand*, **Journal of Allergy and Clinical Immunology,** *130*(5) 2012. https://doi.org/10.1016/J.JACI.2012.08.033

Hanson K. E, Azar M. M, Banerjee R, Chou A, Colgrove R. C, Ginocchio C. C, & ACaliendo A. M, *Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations from the IDSA's Diagnostics Committee,* **Clinical Infectious Diseases,** 71(10), 2020, 2744 -2751.

Harding J. N, Siefker D, Vu L, You D, De. Vincenzo J, Pierre J. F, & Cormier S. A, *Altered Gut Microbiota in Infants is Associated with Respiratory Syncytial Virus Disease Severity*, **BMC Microbiology,** 20(1), 2020, 1-11.

Hatter L, Eathorne A, Hills T, Bruce P, & Beasley R, *Respiratory Syncytial Virus: Paying the Immunity Debt with Interest,* **The Lancet Child & Adolescent Health**, 5(12), 2021, 44-45.

Hernández-Rivas L, Pedraz T, Calvo C, San Juan I, & Robustillo A, *Respiratory Syncytial Virus Outbreak During the COVILD-19 Pandemic, How Has it Changed?* **Enfermedades Infecciosasy Microbiología Clínica**, 2021.

Hopfer H, Herzig M. C, Gosert R, Menter T, Hench J, Tzankov A, & Miller S. E, Hunting S. *E, Coronavirus by Transmission Electron Microscopy–A Guide to*

SARS-CoV-2-Associated Ultrastructural Pathology in COVID-19 Tissues, **Histopathology**, 78(3), 2021, 358-370.

Hopkins C, *Loss of Sense of Smell as Marker of COVID-19 Infection, Ear, Nose and Throat Surgery Body of United Kingdom, Retrieved March* 28, 2020.

Hosen I, Pakpour A H, Sakib N, Hussain N, Mamun F. A.1, &VMamun M. A, *Knowledge and Preventive Behaviors Regarding COVID-19 in Bangladesh: a Nationwide Distribution*, **PLoS One,** 16(5), 2021, 0251151.

Huang K, Ying T, & Wu Y, *Single-Domain Antibodies as Therapeutics for Respiratory RNA Virus Infections,* **Viruses,** 14(6), 2022, 1162.

Hughes B, Duong D, White B. J, Wigginton K. R, Chan E. M, Wolfe M. K, & Boehm A. B, *Respiratory Syncytial Virus (RSV) RNA in Wastewater Settled Solids Reflects RSV Clinical Positivity Rates,* **Environmental Science & Technology Letters,** 9(2), 2022, 173-178.

Hu M, Schulze K.E, Ghildyal R, Henstridge D.C, Kolanowski J.L, New E.J, Hong Y, Hsu A.C, Hansbro P.M, Wark P.A, Bogoyevitch M.A, Jans D.A, *Respiratory Syncytial Virus Co-opts Host Mitochondrial Function to Favour Infectious Virus Production*, **Elife**, (8), 2019, 3-10.

Hui D. S, Azhar E. I, Madani T. A, Ntoumi F, Kock R, Dar O, & Petersen E, *The Continuing 2019-nCoV Epidemic Threat of Novel CoronaViruses to Global Health-The Latest 2019 Novel CoronaVirus OutBreak in Wuhan, China*, **International Journal of Infectious Diseases**, 91, 2020, 264-266.

Idris O. O, & Kolawole O. M, *SeroPrevalence and Molecular Characterization of Human Respiratory Syncytial Virus and Human AdenoVirus among Children in Ado-Ekiti, Nigeria*, **Journal of Medical Virology**, 94(6), 2022, 2548-2557.

IG Giamberardino H. O, Pacheco A. P, Pereira L. A, Debur M. D. C, Genehold G, & Raboni S. M, *Respiratory Syncytial Virus: Host Genetic Susceptibility and Factors Sssociated with Disease Severity in a Cohort of Pediatric Patients*, **Journal of Tropical Pediatrics**, 68(6), 2022, 091.

J *in Young Children in Primary Care,* **BMC Infectious Diseases**, 21(1), 2021, 1-10.

Jeffree C. E, Rixon H. W. M, Brown, G, Aitken, J, & Sugrue R. J, *Distribution of the Attachment (G) GlycoProtein and GM1 within the Envelope of Mature Respiratory Syncytial Virus Filaments Revealed using Field Emission Scanning Electron Microscopy*, **Virology**, 306(2), 2003, 254–267. https://doi.org/10.1016/S0042-6822(02)00016-8

Jha A, Jarvis H, Fraser C, & Openshaw P. J, *Respiratory Syncytial Virus. In SARS, MERS and other Viral Lung Infections,* 2016. *Available at: http://www.ncbi.nlm.nih.gov/pubmed/20399493*

Johnson SM, McNally BA, Ioannidis I, Flano E, Teng MN, Oomens AG, Walsh EE, Peeples ME, *Respiratory Syncytial Virus Uses CX3CR1 as a Receptor on Primary Human Airway Epithelial Cultures*, **PLoS Pathog**, 11(12), 2015, 1005318

Johnson Y., Li. E. K, Shi T, Campbell H, Chaves S. S, Commaille-Chapus C, & Nair H, *National Burden Estimates of Hospitalisations for Acute Lower Respiratory Infections due to Respiratory Syncytial Virus in Young Children in 2019 Among 58 Countries: a Modelling Study,* **The Lancet Respiratory Medicine**, 9(2), 2021, 175-185.

Jackson M. L, Scott E, Kuypers J, Nalla A. K, Roychoudury P, & Chu H, Y, *Epidemiology of Respiratory Syncytial Virus Across Five Influenza Seasons Among Adults and Children One Year of Age and Older—Washington State, 2011/2012–2015/2016*, **The Journal of Infectious Diseases**, 223(1), 2021, 147-156.

Kim J. H, Roh Y. H, Ahn J. G, Kim M. Y, Huh K, Jung J, & Kang J. M, *Respiratory Syncytial Virus and Influenza Epidemics Disappearance in Korea During the 2020–2021 Season of COVID-19*, **International Journal of Infectious Diseases,** 110, 2021, 29-35.

Kuek L. E, & Lee R. J, *First Contact: The Role of Respiratory Cilia in Host-Pathogen Interactions in the Airways*, **American Journal of Physiology-Lung Cellular and Molecular Physiology**, 319(4), 2020, 603-619.

Kalinowski A, Galen BT, Ueki IF, Sun Y, Mulenos A, Osafo-Addo A, Clark B, Joerns J, Liu W, Nadel JA, Dela Cruz CS, Koff JL, *Respiratory Syncytial Virus Activates Epidermal Growth Factor Receptor to Suppress Interferon Regulatory Factor 1-Dependent Interferon-.ambda and Antiviral Defense in Airway Epithelium,* **Mucosal Immunol**. 2018, 11(3), 958-967.

Kamau E, Otieno J. R, Lewa C. S, Mwema A, Murunga N, Nokes D. J, & Agoti C. N, *Evolution of Respiratory Syncytial Virus Genotype BA in Kilifi, Kenya, 15 years on*, **Scientific Reports,** 10(1), 2020**,** 1-12.

Kang Y, Ohnishi T, Yutaka K, Kunikata T, & Ichihashi K, *Decrease in Pediatric Inpatients with Respiratory Syncytial Virus Infection during Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic*, **Pediatrics International**, 64(1), 2022, 3-10.

Kim H. N, Hwang J, Yoon S. Y, Lim C. S, Cho Y, Lee C. K, & Nam M. H, *Molecular Characterization of Human Respiratory Syncytial Virus in Seoul, South Korea, during 10 Consecutive Years, 2010–2019*, **Plos One**, 18(4), 2023, 0283873.

Kim J. H, Kim H. Y, Lee M, Ahn J. G, Baek J. Y, Kim M.Y, & Kang J. M, *Respiratory Syncytial Virus Outbreak Without Influenza in the Second Year of the Coronavirus Disease 2019 Pandemic: A National Sentinel Surveillance in Korea, 2021-2022 Season*, **J. Korean Med. Sci,** 37, 2022, 258.

King T, Mejias A, Ramilo O, Peeples M.E, *The Larger Attachment Glycoprotein of Respiratory Syncytial Virus Produced in Primary Human Bronchial Epithelial Cultures Reduces Infectivity for Cell Lines*, **PLoS Pathog**, 17(4), 2021,1009469.

Krzyzaniak MA, Zumstein MT, Gerez JA, Picotti P, Helenius A, *Host Cell Entry of Respiratory Syncytial Virus Involves Macropinocytosis Followed by Proteolytic Activation of the F Protein*, **PLoS Pathog**, 9(4), 2013,1003309.

Kubale J, Kuan G, Gresh L, Ojeda S, Azziz-Baumgartner E, Sanchez N, & Gordon A, *Assessing the Incidence of Symptomatic Respiratory Syncytial Virus Illness within a Prospective Birth Cohort in Managua, Nicaragua*, **Clinical Infectious Diseases,** 70 (10), 2020, 2029-2035.

Kuitunen I, & Renko M, *Lessons to Learn from the Current Pandemic for Future Non-Pharmaceutical Interventions Against the Respiratory Syncytial Virus–Nationwide Register-Study in Finland*, **Infectious Diseases,** 53(6), 2021, 476-478.

Kumar K. R, Mufti S.S, Sarathy V, Hazarika D, & R. Naik R, An Update on Advances in COVID-19 Laboratory Diagnosis and Testing Guidelines in India, **Frontiers in Public Health**, 9, 2021, 568603.

Kurt-Jones E. A, Popova L, Kwinn L, Haynes L. M, Jones L. P, Tripp R. A, Walsh E. E, Freeman M. W, Golenbock D. T, Anderson L. J, Finberg R. W, *Pattern Recognition Receptors TLR4 and CD14 Mediate Response to Respiratory Syncytial Virus,* **Nature Immunology**,1(5), 2000, 398-401.

Kushner L. E, Schroeder A. R, Kim J, & Mathew R, *"For COVID" or "With COVID", Classification of SARS-CoV-2 Hospitalizations in Children,* **Hospital Pediatrics**, 11(8), 2021, 151-156.

Kutsaya A, Teros-Jaakkola T, Kakkola L, Toivonen L, Peltola V, Waris M, & Julkunen I, *Prospective Clinical and Serological Follow-Up in Early Childhood Reveals a High Rate of Subclinical RSV Infection and a Relatively High Reinfection Rate within the First 3 years of Life,* **Epidemiology & Infection**, 144(8), 2021, 1622-1633.

Laenger F. P, Schwerk N, Dingemann J, Welte T, Auber B, Verleden S, & Jonigk D, *Interstitial Lung Disease in Infancy and Early Childhood: Clinicopathological Primer*, **European Respiratory Review**, 31, 2022, 163.

Laubreton D, Drajac, Eléouët J. F, Rameix-Welti M. A, Lo-Man R, Riffault S, & Descamps D, *Regulatory B Lymphocytes Colonize the Respiratory Tract of Neonatal Mice and Modulate Immune Responses of Alveolar Macrophages to RSV Infection in IL-10-Dependant Manner*, **Viruses**, 12(8), 2020, 822.

Lay, M. K., González, P. A., León, M. A., Céspedes, P. F., Bueno, S. M., Riedel, C. A., & Kalergis, A. M., *Advances in Understanding Respiratory Syncytial Virus Infection in Airway Epithelial Cells and Consequential Effects on the Immune Response,* **Microbes and Infection,** 15(3), 2013, 230–242. https://doi.org/10.1016/J.MICINF.2012.11.012

Le Bert N, Tan A.T, Kunasegaran K, Tham C. Y, Hafezi M, & Bertoletti A, *SARS-CoV-2-Specific T Cell Immunity in Cases of COVID-19 and SARS, and Uninfected Controls,* **Nature**, 584(7821), 2020, 457-462.

Lee M, & M. You. *Psychological and Behavioral Responses in South Korea during the Early Stages of Coronavirus Disease 2019 (COVID-19),* **Int J Environ Res Public Health**, 17(9), 2020, 2977.

Liesman, R. M., Buchholz, U. J., Luongo, C. L., Yang, L., Proia, A. D., DeVincenzo, J. P., Collins, P. L., & Pickles, R. J. (2014), *RSV-encoded NS2 Promotes Epithelial Cell Shedding and Distal Airway Obstruction,* **Journal of Clinical Investigation**, 124(5), 2219–2233. https://doi.org/10.1172/JCI72948

Li H. M, R., Ghildyal R, Hu M, Tran K. C, Starrs L. M, Mills J, & Jans D, *A Respiratory Syncytial Virus Matrix Protein-Chromatin Association is Key to Transcriptional Inhibition in Infected Cells,* **Cells,** 10(10), 2021, 2786.

Lingemann M, McCarty T, Liu X, Buchholz UJ, Surman S, Martin SE, Collins PL, Munir S. *The Alpha-1 Subunit of the Na+,K+-ATPase (ATP1A1) is Required for Macropinocytic Entry of Respiratory Syncytial Virus (RSV) in Human Respiratory Epithelial Cells*, **PLoS Pathog**, 15(8), 2019, 1007963.

Li P, Zhang Y, Shen W, Shi S, & Zhao Z, dbGSRV, *A Manually Curated Database of Genetic Susceptibility to Respiratory Virus,* **Plos One**, 17(3), 2022, 0262373.

Linnakoski R, Sutela S, Coetzee M. P, Duong T. A, Pavlov I. N, Litovka Y. A, & Vainio E. J, Armillaria Root Rot Fungi Host Single-Stranded RNA Viruses, **Scientific Reports,** 11(1), 2021, 7336.

Liua H, Wanga LL, Zhaoa SJ, Kwak-Kimb J, Mord G, AH. Liaoa, *Why are Pregnant Women Susceptible to COVID-19? An Immunological Viewpoint,* **J Reprod Immunol**, 139, 2020, 103122.

Liu, L., Oza, S., Hogan, D., Perin, J., Rudan, I., Lawn, J. E., Cousens, S., Mathers, C., & Black, R. E., *Global, Regional, and National Causes of Child Mortality in 2000-13, with Projections to Inform Post-2015 Priorities: An Updated Systematic Analysis*, **The Lancet**, 385(9966), 2015, 430–440. https://doi.org/10.1016/S0140-6736(14)61698-6

Loeffelholz M. J, & Tang Y. W, *Laboratory Diagnosis of Emerging Human Coronavirus Infections–The State of the Art*, **Emerging Microbes & Infections,** 9(1), 2020**,** 747-756.

Lopes B. R. P, da Silva G. S, de Lima Menezes G, de Oliveira J, Watanabe A. S. A, Porto B. N, & Toledo K., *A Serine Proteases in Neutrophil Extracellular Traps Exhibit Anti-Respiratory Syncytial Virus Activity*, **International Immunopharmacology,** 106, 2022 108573.

Lorfa S. K, Ottu I. F, Oguntayo R, Ayandele O, Kolawole S.O, & Olapegba P. O, *COVID-19 Knowledge, Risk Perception, and Precautionary Behavior among Nigerians: A Moderated Mediation Approach*, **Frontiers in Psychology**, 11, 2020, 3292.

Lotfi M, Hamblin M. R, & Rezaei N., COVID-19: *Transmission, Prevention, and Potential Therapeutic Opportunities*, **Clinica Chimica Acta**, 508, 2020, 254– 266.

Lai C, C, Shih T. P, & Tang, W. C., Ko, H. J. Hsueh P. R, *Severe Acute esRpiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease-2019 (COVID-19): The pidemic and the Challenges*, **International Journal of Antimicrobial Agents,** 55(3), 2020, 105924.

Lane S, Hilliam Y, & Bomberger J. M, *Microbial and Immune Regulation of the Gut-Lung Axis during Viral-Bacterial Coinfection*, **Journal of Bacteriology**, 205(1), 2023, 00295-22.

Lee, H. C., Headley, M. B., Loo, Y. M., Berlin, A., Gale, M., Debley, J. S., Lukacs, N. W., & Ziegler, S.F., *Thymic Stromal Lymphopoietin is Induced by Respiratory Syncytial Virus-Infected Airway Epithelial Cells and Promotes a Type 2 Response to Infection,* **Journal of Allergy and Clinical Immunology,** 130(5), 2012, 2-10. https://doi.org/10.1016/J.JACI.2012.07.031

Lee J-T, Chang L-Y, Wang L-C, Kao C-L, Shao P-L, Lu C-Y, Lee P-I, Chen J-M, Lee C-Y, Huang L-M., *Epidemiology of Respiratory Syncytial Virus Infection in Northern Taiwan, 2001-2005 — Seasonality, Clinical Characteristics, and Disease Burden*, **J Microbiol Immunol Infect**, 40, 2007, 293-301.

Letafati A, Aghamirmohammadali F. S, Rahimi-Foroushani A, Hasani S. A, Mokhtari-Azad T, & Yavarian J, *No Human Respiratory Syncytial Virus but SARS-CoV-2 Found in Children under 5 years old Referred to Children Medical Center in 2021, Tehran, Iran*, **Journal of Medical Virology**, 94(7), 2022, 3096-3100.

Leung E. C. M, V. C. Y, Chow, M. K. P, Lee, K. P. S, Tang, D. K. C, Li, & Lai R. W. M, *Evaluation of the Xpert Xpress SARS-CoV-2/Flu/RSV Assay for Simultaneous etection of SARS-CoV-2, Influenza A and B Viruses, and Respiratory Syncytial Virus in Nasopharyngeal Specimens*, **Journal of Clinical Microbiology**, 59(4), 2021, 02965-20.

Linssen R. S, Bem R. A, Kapitein B, Rengerink K. O, Otten M. H, den Hollander B, & PICE *Study Group M. Wösten-van Asperen Roelie H. Klein Richard C.J Kneyber Martin Kuiper Jan Willem Verlaat Carin van Heerde Marc A. Riedijk Maaike A. van Waardenburg Dick. Burden of Respiratory Syncytial Virus Bronchiolitis on the Dutch Pediatric Intensive Care Units*, **European Journal of Pediatrics**, 180(10), 2021, 3141-3149.

Malekshahi S.S, Samieipour Y, Rahbarimanesh A. A, Izadi A, Ghavami N, Razaghipour S, & Salimi V, *Genetic Characterization of G Protein in Respiratory Syncytial Virus ON-1 genotype in Tehran*, **Future Virology,** 15(11), 2020, 725-734.

Mebratu Y. A, & Tesfaigzi Y, Is IL-1β *A Target for Reducing Hospitalization of Infants Infected with Respiratory Syncytial Virus*, **American Journal of Respiratory Cell and Molecular Biology**, 66(3), 2022**,** 248-249.

Meyer M, Ruebsteck E, Eifinger F, Klein F, Oberthuer A, van Koningsbruggen-Rietschel S, & Weber L. T, *Morbidity of Respiratory Syncytial Virus (RSV) Infections: RSV Compared With Severe Acute Respiratory Syndrome Coronavirus 2 Infections in Children Aged 0–4 Years in Cologne, Germany*, **The Journal of Infectious Diseases**, 226(12), 2022, 2050-2053.

Mohamad E, & Azlan A., *A COVID-19 and Communication Planning for Health Emergencies. Jurnal Komunikasi*, **Malaysian Journal of Communication,** 36(1), 2020, 3-10.

Mohebi L, Karami H, Mirsalehi, Ardestani N. H, Yavarian J, Mard-Soltani M, & Salimi V, *A Delayed Resurgence of Respiratory Syncytial Virus (RSV) During the COVID-19 Pandemic: An Unpredictable Outbreak in a Small Proportion of Children in the Southwest of Iran, April 2022*, **Journal of Medical Virology**, 94(12), 2022, 5802-5807.

Mostafa H. H, Carroll K. C, Hicken R, Berry G. J, Manji R, Smith E, & Loeffelholz M. J, *Multicenter Evaluation of the Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV Test*, **Journal of Clinical Microbiology**, 59(3), 2021, 02955-20.

Malinczak C. A, Lukacs N. W, & Fonseca W, *Early-Life Respiratory Syncytial Virus Infection, Trained Immunity and Subsequent Pulmonary Diseases*, **Viruses**, 12(5), 2020, 505.

Malhotra R, Ward M, Bright H, Priest R, Foster Martyn R, Hurle M, Blair E, Bird M, *Isolation and Characterisation of Potential Respiratory Syncytial Virus Receptor(s) on Epithelial Cells*, **Microbes Infect**, 5(2), 2003, 23-133.

Manuel O, Estabrook M, & *American Society of Transplantation Infectious Diseases Community of Practice*, *RNA Respiratory Viral Infections in Solid Organ Transplant Recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice*, **Clinical Transplantation**, 33(9), 2019, 13511.

Marty, F. M., Chemaly, R. F., Mullane, K. M., Lee, D. G., Hirsch H, Small C B, & Dadwal, S. S., *A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multicenter Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of Presatovir in Hematopoietic Cell Transplant Recipients with Respiratory Syncytial Virus Infection of the Lower Respiratory Tract*, **Clinical Infectious Diseases**, 71(11), 2020, 2787-2795.

Mastrangelo, P., Norris, M. J., Duan, W., Barrett, E. G., Moraes, T. J., & Hegele, R. G., *Targeting Host Cell Surface Nucleolin for RSV Therapy: Challenges and Opportunities*, **Vaccines**, 5(3), 2017, 3-10. https://doi.org/10.3390/VACCINES5030027

Mazet J. A, Genovese B. N, Harris L. A, Cranfield M, Noheri J. B, Kinani J. F, & Gilardi K. V, *Human Respiratory Syncytial Virus Detected in Mountain Gorilla Respiratory Outbreaks*, **EcoHealth**, 17, 2020, 449-460.

McNab S, Ha Do L. A, Clifford V, Crawford N. W, Daley A, Mulholland K, & Wurzel D, *Changing Epidemiology of Respiratory Syncytial Virus in Australia—Delayed Re-Emergence in Victoria Compared to Western Australia/New South Wales (WA/NSW) After Prolonged Lock-Down for Coronavirus Disease 2019 (COVID-19)*, **Clinical Infectious Diseases,** 73(12), 2021, 2365-2366.

Mejias A, Rodríguez-Fernández R, Oliva, Peeples M. E, & Ramilo O, *The Journey to a Respiratory Syncytial Virus Vaccine*, **Annals of Allergy, Asthma & Immunology**, 125(1), 2020, 36-46.

Melebari S, *Etiology of Respiratory Infections among Neonatal and Pediatric Inpatients in a Tertiary Hospital in Makkah, Saudi Arabia,* **EC Pediatrics,** 11, 2022, 24-32.

Mittal P, Kapoor R, Saharan A, & Gautam R.K, *Targeting Molecular and Cellular Mechanisms in Respiratory Syncytial Virus (RSV) Infection,* **Targeting Cellular Signalling Pathways in Lung Diseases**, 3, 2021**,** 501-516.

Miyama T, Iritani N, Nishio T, Ukai T, Satsuki Y, Miyata H, & Kobayashi K, *Seasonal Shift in Epidemics of Respiratory Syncytial Virus Infection in Japan,* **Epidemiology & Infection**, 2, 2021, 149.

MNowalk M. P, D'Agostino H, Dauer K, Stiegler M, Zimmerman R. K, & Balasubramani G. K, *Estimating the Burden of Adult Hospitalized RSV Infection Including Special Populations*, **Vaccine,** 40(31), 2022, 1-2.

Modreg A, arlero D, Arranz R, & Martín-Benito J, *CryoEM of Viral Ribonucleoproteins and Nucleocapsids of Single-Stranded RNA Viruses*, **Viruses**, 15(3), 2023, 653.

Mogensen T. H, Genetic Susceptibility to Viral Disease in Humans, **Clinical Microbiology and Infection**, 3, 2022, 1-2.

Molteni M, Gemma S, Rossetti C., *The Role of Toll-Like Receptor 4 in Infectious and Noninfectious Inflammation*, **Mediators Inflamm**, 2, 2016, 6978936.

Morris DR, Qu Y, Agrawal A, Garofalo RP, Casola A., *HIF-1α Modulates Core Metabolism and Virus Replication in Primary Airway Epithelial Cells Infected with Respiratory Syncytial Virus*, **Viruses**, 12(10), 2020, 1-2.

Munkstrup C, Lomholt F. K, Emborg H. D, Møller K. L, Krog J. S, Trebbien R, & Vestergaard L. S, *Early and Intense Epidemic of Respiratory Syncytial Virus (RSV) in Denmark, August to December 2022*, **Eurosurveillance**, 28(1), 2023, 2200937.

Muñoz-Escalante J. C, Comas-García A, Bernal-Silva S, Robles-Espinoza C. D, Gómez-Leal G, & Noyola D.E, *Respiratory Syncytial Virus A Genotype Classification Based on Systematic Intergenotypic and Intragenotypic Sequence, Analysis*, **Scientific Reports**, 9(1), 2019, 1-12.

Munteanu A. N, Surcel M, Huică R. I, Isvoranu G, Constantin C, Pîrvu I. R, & Neagu M, *Peripheral Immune Cell Markers in Children with Recurrent Respiratory Infections in the Absence of Primary Immunodeficiency*, **Experimental and Therapeutic Medicine**, 18(3), 2019, 1693-1700.

Nam H. H, & Ison M G, *Respiratory Syncytial Virus*, **Seminars in Respiratory and Critical Care Medicine**, 42(06), 2021, 788-799.

Nam H. H, & Ison M. G, Respiratory Syncytial Virus Infection in Adults, ***Bmj,*** *366,* 2019, 2.

Nascimento-Carvalho, A. C., Ruuskanen, O., & Nascimento-Carvalho, C. M., *Comparison of the Frequency of Bacterial and Viral Infections Among Children with Community-Acquired Pneumonia Hospitalized Across Distinct Severity Categories*: *A Prospective Cross-Sectional Study,* **BMC Pediatrics**, 16(1), 2016, 3-10. https://doi.org/10.1186/S12887-016-0645-3

Naseef H.A, Hadba L.S, & Humos L.A., *Knowledge, Attitudes and Practices About Coronavirus Disease (COVID-19) Among Birzeit University Students: A Cross-Sectional Study, 2,* 2022, 2.

Nathan A. M, The C. S. J, Jabar K.A, Teoh B. T, Tangaperumal A, Westerhout C, & de Bruyne J. A, *Bacterial Pneumonia and its Associated Factors in Children from A Developing Country: A Prospective Cohort Study*, **PloS One**, 15(2), 2020, 0228056.

Nachega J. B, Atteh R, Ihekweazu C, Sam-Agudu N. A, Adejumo P, & Kilmarx P. H, *Contact Tracing and the COVID-19 Response in Africa: Best Practices, Key Challenges, and Lessons Learned from Nigeria, Rwanda, South Africa, and Uganda*, **The American Journal of Tropical Medicine and Hygiene**, 104(4), 2021, 1179.

Nisole S, Said EA, Mische C, Prevost MC, Krust B, Bouvet P, Bianco A, Briand JP, Hovanessian AG, *The Anti-HIV Pentameric Pseudopeptide HB-19 Binds the C-Terminal End of Nucleolin and Prevents Anchorage of Virus Particles in the Plasma Membrane of Target Cells*, **The Journal of Biological Chemistry**, 277(23), 2002, 20877-20886.

Norman P, Wilding S, & Conner M, *Reasoned Action Approach and Compliance with Recommended Behaviours to Prevent the Transmission of the SARS-CoV-2 Virus in the UK*, **British Journal of Health Psychology**, 25, 2020, 1006–1019.

Nwonwu E.U, Ossai E.N, Umeokonkwo C.D, & Ituma I.B, *Knowledge and Preventive Practice to COVID-19 Among Household Heads in Enugu Metropolis, South-East Nigeria*, **The Pan African Medical Journal**, 37, 2020, 3-10.

Omotoso O.E, Omotoso E.F, Paimo K.O, Teibo J.O, & Olagunju A.O, *Knowledge and Adherence to COVID-19 Preventive Measures: A Continental Review*, **Sudan Journal of Medical Sciences**, 16(3), 2021, 371-385.

Omotoso O. E., *Contributory Role of SARS-CoV-2 Genomic Variations and Life*, **The Pan African Medical Journal,** 100, 2020, 123.

Ozdemir S, Chaudhry S, Ng, I, & Finkelstein E. A, *Adoption of Preventive Behaviour Strategies and Public Perceptions About COVID-19 in Singapore*, **International Journal of Heal Policy Management**, 2, 2020, 1-2.

Ohashi E, Hayakawa I, Murofushi Y, Kawai M, Suzuki-Muromoto S, Abe Y, & Kubota M, *Recurrent Acute Necrotizing Encephalopathy in a Boy with RANBP2 Mutation and Thermolabile CPT2 Variant: The First Case of ANE1 in Japan*, **Brain and Development**, 43(8), 2021, 873-878.

Olsen S. J, Winn A. K, Budd A. P, Prill M. M, Steel J, Midgley C. M, & Silk B.J, *Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic—United States, 2020–2021*, **Morbidity and Mortality Weekly Report**, 70(29), 2021, 1013.

Opek M.W, Yeshayahu Y, Glatman-Freedman A, Kaufman Z, Sorek N, & Brosh- Nissimov T, *Delayed Respiratory Syncytial Virus Epidemic in Children After Relaxation of COVID-19 Physical Distancing Measures, Ashdod, Israel,* **Eurosurveillance,** 26(29), 2021, 2100706.

Ortiz Moyano R, Raya Tonetti F, Tomokiyo M, Kanmani P, Vizoso-Pinto M. G. H., KiV, & Villena J, *The Ability of Respiratory Commensal Bacteria to Beneficially Modulate the Lung Innate Immune Response is a Strain Dependent Characteristic,* **Microorganisms**, *8*(5), 2020**,** 727.

Ohnishi T., & Kawano, Y., *Resurgence of Respiratory Syncytial Virus Infection During an Atypical Season in Japan*, **Journal of the Pediatric Infectious Diseases Society**, 10(10) 2021, 982-983.

Pandya M. C, Callahan S.M, Savchenko K. G, & Stobart C. C, *A Contemporary View of Respiratory Syncytial Virus (RSV) Biology and Strain-Specific Differences*, **Pathogens**, 8(2) 2019, 67.

Papan C, Willersinn M, Weiß C, Karremann M, Schroten H, &TenenbaumT, *Antibiotic Utilization in Hospitalized Children Under 2 years of Age with Influenza or Respiratory Syncytial Virus Infection–A Comparative, Retrospective Analysis*, **BMC Infectious Diseases,** 20(1), 2020, 1-10.

Persson B. D, Jaffe A. B, Fearns R, & Danahay H, *Respiratory Syncytial Virus can Infect Basal Cells and Alter Human Airway Epithelial Differentiation,* **PLoS ONE**, 9(7) 2014, 2. https://doi.org/10.1371/JOURNAL.PONE.0102368

Pecora F, Persico F, Argentiero A, Neglia C, & Esposito S, *The Role of Micronutrients in Support of the Immune Response Against Viral Infections*, **Nutrients**, 12(10), 2020, 3198.

Pappa S, Haidopoulou K, Zarras C, Theodorakou E, Papadimitriou E, Iosifidis E, & A. Papa, *Early Initiation of the Respiratory Syncytial Virus Season in 2021–2022*, *Greece*, **Journal of Medical Virology,** 94(7), 2022, 3453-3456.

Pellegrinelli L, Galli C, Bubba L, Cereda D, Anselmi G, Binda S, & Pariani E, *Respiratory Syncytial Virus in Influenza-Like Illness Cases: Epidemiology and Molecular Analyses of Four Consecutive Winter Seasons (2014-2015/2017-2018) in Lombardy (Northern Italy),* **Journal of Medical Virology**, 9 (12), 2020, 2999-3006.

Pickles R. J, & DeVincenzo J. P., *Respiratory Syncytial Virus (RSV) and its Propensity for Causing Bronchiolitis,* **The Journal of Pathology,** *235*(2), 2015, 266–276. https://doi.org/10.1002/PATH.4462

Piedimonte, G., & Perez, M. K., *Respiratory Syncytial Virus Infection and Bronchiolitis, Pediatrics in Review,* 35(12), 2014, *519–530*. https://doi.org/10.1542/PIR.35-12-519

Pscheidt V. M, Gregianini T. S, Martins L. G, & Veiga A. B. G. D, *Epidemiology of Human Adenovirus Associated with Respiratory Infection in Southern Brazil,* **Reviews in Medical Virology,** 31(4), 2021, 2189.

Puthothu B, Krueger M, Heinze J, Forster J, & Heinzmann A, *Impact of IL8 and IL8-Receptor Alpha Polymorphisms on the Genetics of Bronchial Asthma and Severe RSV Infections*, **Clinical and Molecular Allergy**, 4(2), 2006, 1-6.

Qiao, J., Li, A., & Jin, X., TSLP from RSV-Stimulated Rat Airway Epithelial Cells Activates Myeloid Dendritic Cells, *Immunology and Cell Biology*, 89(2), 2011, 231–238. https://doi.org/10.1038/ICB.2010.85

Rajan A, Weaver A. M, Aloisio G. M, Jelinski J, Johnson H. L, Venable S. F, & Piedra P. A, *The Human Nose Organoid Respiratory Virus Model: An Ex Vivo Human Challenge Model to Study Respiratory Syncytial Virus (RSV) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pathogenesis and Evaluate Therapeutics*, **Mbio,** 13(1), 2022, 03511-21.

Rawling J, Cano O, Garcin D, Kolakofsky D, & Melero J. A, *Recombinant Sendai Viruses Expressing Fusion Proteins with Two Furin Cleavage Sites Mimic the Syncytial and Receptor-Independent Infection Properties of Respiratory Syncytial Virus*, **Journal of Virology**, *85*(6), 2011, 2771–2780. https://doi.org/10.1128/JVI.02065-10

Ribeiro B. V, Cordeiro T. A. R, e Freitas G. R. O, Ferreira L F, & Franco D. L, *Biosensors for the Detection of Respiratory Viruses: A Review*, **Talanta Open**, 2, 2020, 100007.

Rohaim M. A, Naggar R F E1, Clayton E, & Munir M, *Structural and Functional Insights Into Non-Structural Proteins of Coronaviruses*, **Microbial Pathogenesis,** 150, 2021, 104641.

Rossi G. A, Ballarini S, Silvestri M, Sacco O, & Colin A. A, *Respiratory Syncytial Virus and Airway Microbiota–A Complex Interplay and Its Reflection on Morbidity*, **Pediatric Allergy and Immunology,** 32(6), 2021, 1141-1151.

Rosemary M., Klein L *et al; The Interception of Sex and Gender in theTtreatment of Influenza*, **Curr Opin Virol**, (35), 2019, 35-41

Rayavara K, Kurosky A, Stafford S. J, Garg N. J, Brasier A. R, Garofalo R. P, & Hosakote Y. M, *Proinflammatory Effects of Respiratory Syncytial Virus–Induced Epithelial HMGB1 on Human Innate Immune Cell Activation*, **The Journal of Immunology**, 201(9), 2018, 2753–2766. https://doi.org/10.4049/JIMMUNOL.1800558

Resch B, Puchas, Resch E, & Urlesberger B, *Epidemiology of Respiratory Syncytial Virus–Related Hospitalizations and the Influence of Viral coinfections in Southern Austria in a 7-year Period,* **The Pediatric Infectious Disease Journal**, 39(1), 2020, 12-16.

Rybak A, Levy C, Jung C, Béchet S, Batard C, Hassid F, & Cohen R, *Delayed Bronchiolitis Epidemic in French Primary Care Setting Driven by Respiratory Syncytial Virus: Preliminary Data from the Oursyn Study,* **The Pediatric Infectious Disease Journal,** 40(12), 2021, 511-514.

San-Juan-Vergara H, Sampayo-Escobar V, Reyes N, Cha B, Pacheco-Lugo L, Wong T, Peeples M.E, Collins P.L, Castaño M.E, Mohapatra S.S, *Cholesterol-Rich Micro Domains as Docking Platforms for Respiratory Syncytial Virus in Normal Human Bronchial Epithelial Cells,* **J Virol**, 86(3), 2012,1832-1843.

Schmoele-Thoma B, Zareba A. M, Jiang Q, Maddur M. S, Danaf R, Mann A, & Swanson K. A, *Vaccine Efficacy in Adults in a Respiratory Syncytial Virus Challenge Study*, **New England Journal of Medicine,** 386(25), 2022**,** 2377-2386.

Shaw E. R, & Su H. C, *The Influence of Immune Immaturity on Outcome After Virus Infections* **The Journal of Allergy and Clinical Immunology: In Practice,** 9(2), 2021, 641-650.

Su P. Y, Wang Y. F, Huang S. W, Lo Y. C, Wang Y. H, Wu S. R, Shieh D. B, Chen S. H, Wang J. R, Lai M. D, Chang C. F, *Cell Surface Nucleolin Facilitates Enterovirus 71 Binding and Infection,* **J Virol**, 89(8), 2015, 4527-4538.

Salimi V, Viegas M, Trento A, Agoti C. N, Anderson L. J, Avadhanula V, & Buchholz U. J, *Proposal for Human Respiratory Syncytial Virus Nomenclature Below the Species Level*, **Emerging Infectious Diseases**, 27(6), 2021, 2.

Sastre P, Oomens A. G. P, & Wertz G.W., *The Stability of Human Respiratory Syncytial Virus is Enhanced by Incorporation of the Baculovirus GP64 Protein*, **Vaccine**, 25(27), 2007, 5025–5033. https://doi.org/10.1016/j.vaccine.2007.04.066

Saravia J, You D, Shrestha B, Jaligama S, Siefker D, Lee G. I, Harding J. N, Jones T. L, Rovnaghi C, Bagga B, DeVincenzo J. P, Cormier S. A, *Respiratory Syncytial Virus Disease Is Mediated by Age-Variable IL-33*, **PLoS Pathog**, 11(10), 2015, 1005217.

Scaggs Huang F, Bernstein D I, Slobod K.S, Portner A, Takimoto T, Russell C.J, & Hurwitz J.L, *Safety and Immunogenicity of an Intranasal Sendai Virus-Based Vaccine for Human Parainfluenza Virus Type I and Respiratory Syncytial Virus (SeVRSV) in Adults*, **Human Vaccines & Immunotherapeutics**, 17(2), 2021, 554-559.

Schadenhofer A, *Respiratory Syncytial Virus Reverse Genetics for Identification of Molecular Determinants of Strain Specific Phenotypic Changes* ***Doctoral Dissertation****, Dissertation, Hannover, Tierärztliche Hochschule Hannover,* 2, 2021, 1.

Schwartz D. A, & Dhaliwal A, *Infections in Pregnancy with COVID-19 and Other Respiratory RNA Virus Diseases are Rarely, If Ever, Transmitted to the Fetus: Experiences with Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and Influenza*, **Archives of Pathology & Laboratory Medicine**, 144(8), 2020, 920-928.

Sitthicharoenchai P, Alnajjar S, & Ackermann M. R, *A Model of Respiratory syncytial Virus (RSV) Infection of Infants in Newborn Lambs*, **Cell and Tissue Research,** 380, 2020, 313-324.

Song D. XZ. S, Qin X. Q, Xiang Y, Qu X. P, Liu H. J, & Liu C, *Research Progress of Respiratory Syncytial Virus (RSV) Infection and Respiratory Diseases in Infancy,* **Sheng Li Xue Bao*:* [Acta Physiologica Sinica]**, 2021, *73*(6), 1043-1053.

Sosa J. P, Caceres M. M. F, Comptis J. R, Quiros J, Príncipe-Meneses F. S, Riva-Moscoso A, & Marian S, *Effects of Interferon Beta in COVID-19 Adult Patients: Systematic Review,* **Infection & chemotherapy,** 53(2), 2021, 247.

Srikantiah P, Vora P, & Klugman K. P, *Assessing the Full Burden of Respiratory Syncytial Virus in Young Infants in Low-and Middle-Income Countries: The Importance of Community Mortality Studies*, **Clinical Infectious Diseases,** *73*(3), 2021, 177-179.

Staadegaard L, Caini S, Wangchuk S, Thapa B, de Almeida W, A, F, de Carvalho F, C, & Paget J, *The Global Epidemiology of RSV in Community and Hospitalized Care: Findings From 15 Countries,* **In Open Forum Infectious Diseases,** 8(7), 2021, 159.

Staadegaard L, Caini S, Wangchuk S, Thapa B, de Almeida W. A. F, de Carvalho F. C, & Paget J, *Defining the Seasonality of Respiratory Syncytial Virus Around the World: National and Subnational Surveillance Data from 12 Countries,* **Influenza and Other Respiratory Viruses,** 15(6), 2021, 732-741.

Stambas J, Lu C, & Tripp R. A, *Innate and Adaptive Immune Responses in Respiratory Virus Infection: Implications for the Clinic,* **Expert Review of Respiratory Medicine,** 14(11), 2020, 1141-1147.

Stokstad M, Klem T. B, Myrmel M, Oma V. S, Toftaker I, Østerås O, & Nødtvedt A, *Using Biosecurity Measures to Combat Respiratory Disease in Cattle: The Norwegian Control Program for Bovine Respiratory Syncytial Virus and Bovine Coronavirus*, **Frontiers in Veterinary Science**, 7, 2020, 167.

Su J. M, Wilson M. Z, Samuel C. E, & Ma D, *Formation and Function of Liquid-Like Viral Factories in Negative-Sense Single-Stranded RNA Virus Infections*, **Viruses,** 13(1), 2021, 126.

Sun Y. P, Lei S. Y, Wang Y. B, Wang Y. Z, Qiang H. S Yin Y. F, & Xia N. S, *Molecular Evolution of Attachment Glycoprotein (G) and Fusion Protein (F) Genes of Respiratory Syncytial Virus ON1 and BA9 Strains in Xiamen, China*, **Microbiology Spectrum,** 10(2), 2022, 02083-21.

Suryadevara M, & Domachowske J.B, *Epidemiology and Seasonality of Childhood Respiratory Syncytial Virus Infections in the Tropics,* **Viruses**, 13(4), 2021, 696.

Sutto-Ortiz P, Tcherniuk S, Ysebaert N, Abeywickrema P, Noël M, Decombe A. & Decroly E, *The Methyltransferase Domain of the Respiratory Syncytial Virus L Protein Catalyzes Cap N7 and 2'-O-Methylation,* **PLoS Pathogens,** 17(5), 2021, 1009562.

Swanson K.A, Rainho-Tomko J.N, Williams Z.P, Lanza L, Peredelchuk M, Kishko M, & Nabel G. J, *A Respiratory Syncytial Virus (RSV) F Protein Nanoparticle Vaccine Focuses Antibody Responses to a Conserved Neutralization Domain*, **Science Immunology,** 5(47), 2020, 6466.

Tayyari F, Marchant D, Moraes TJ, Duan W, Mastrangelo P, Hegele RG, *Identification of Nucleolin as a Cellular Receptor for Human Respiratory Syncytial Virus,* **Nat Med**, 17(9), 2011, 1132-1135.

Tempia S, Walaza S, Bhiman J. N, McMorrow M. L, Moyes J, Mkhencele T, & Cohen C, *Decline of Influenza and Respiratory Syncytial Virus Detection in Facility-Based Surveillance During the COVID-19 Pandemic, South Africa, January to October 2020,* **Eurosurveillance**, 26(29), 2021, 2001600.

Tenenbaum T, Doenhardt M, Diffloth N, Berner R, & Armann J. P, *High Burden of RSV Hospitalizations in Germany 2021–2022,* **Infection,** 50(6), 2022, 1587-1590.

Tokuhara D, & Hikita N, Cord Blood-Based Approach to Assess Candidate Vaccine Adjuvants Designed for Neonates and Infants, **Vaccines,** 9(2), 2021, 95.

Tabor D. E, Fernandes D. E, Langedijk A. C, Wilkins D, Lebbink R. J, Tovchigrechko A, & Abram M. E, *Global Molecular Epidemiology of Respiratory Syncytial Virus from the 2017− 2018 INFORM-RSV Study*, **Journal of Clinical Microbiology,** 59(1), 2020, 01828-20.

Takashima M. D, Grimwood K, Sly P. D, Lambert S. B, Chappell K. J, Watterson D, & Ware R. S, *Epidemiology of Respiratory Syncytial Virus in a Community Birth Cohort of Infants in the First 2 years of Life,* **European Journal of Pediatrics**, 180, 2021, 2125-2135.

Teirlinck A.C, Broberg E.K, Berg A.S, Campbell H, Reeves R.M, Carnahan A, & Fischer T. K, *Recommendations for Respiratory Syncytial Virus Surveillance at the National Level*, **European Respiratory Journal**, 58(3), 2021, 1.

Techaarpornkul S, Barretto N, Peeples M. E, *Functional Analysis of Recombinant Respiratory Syncytial Virus Deletion Mutants Lacking the Small Hydrophobic and/or Attachment Glycoprotein Gene,* **J Virol**, 75(15), 2001, 6825-6834.

Teo Q. W, van Leur S. W, & Sanyal S, *Escaping the Lion's Den: Redirecting Autophagy for Unconventional Release and Spread of Viruses*, **The FEBS Journal,** 288(13), 2021 3913-3927.

Thielen B. K, Bye E, Wang X, Maroushek S, Friedlander H, Bistodeau S, & Lynfield R, *Summer Outbreak of Severe RSV-B Disease, Minnesota, 2017 Associated with Emergence of a Genetically Distinct Viral Lineage*, **The Journal of Infectious Diseases,** 222(2), 2020, 288-297

Thomas E, Mattila J. M, Lehtinen P, Vuorinen T, Waris M, & Heikkinen T, *Burden of Respiratory Syncytial Virus Infection During the First year of Life*, **The Journal of Infectious Diseases**, 223(5), 2021, 811-817.

Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, & Zhang K, *Characteristics of COVID-19 Infection in Beijing*, **Journal of Infection,** 80(4), 2020, 401-406.

Ujiie M, Tsuzuki S, Nakamoto T, & Iwamoto N, *Resurgence of Respiratory Syncytial Virus Infections During COVID-19 Pandemic, Tokyo, Japan*, **Emerging Infectious Diseases,** 27(11), 2021, 2969.

Van Erp E. A, Lakerveld A. J, de Graaf E, Larsen M. D, Schepp R. M, Hipgrave Ederveen A. L, & van Kasteren P. B, *Natural Killer Cell Activation by Respiratory Syncytial Virus-Specific Antibodies is Decreased in Infants with Severe Respiratory Infections and Correlates with Fc-Glycosylation*, **Clinical & Translational Immunology,** 9(2), 2020, 1112.

Van Summeren J, Meijer A, Aspelund G, Casalegno J. S, Erna G, Hoang U, & Paget J, *Low Levels of Respiratory Syncytial Virus Activity in Europe During the 2020/21 Season: What can we Expect in the Coming Summer and Autumn/Winter?* **Eurosurveillance**, 26(29), 2021, 2100639.

Van Summeren J. J. G. T, Rizzo C, Hooiveld M, Korevaar J. C, Hendriksen J. M. T, Dückers L. M. S, & Paget J, *Evaluation of a Standardized Protocol to Measure the Disease Burden of Respiratory Syncytial Virus Infection in Young Children in Primary Care*, **BMC Infectious Diseases**, 21(1), 2021, 1-10.

Verhoeven D, *Influence of Immunological Maturity on Respiratory Syncytial Virus-Induced Morbidity in Young Children*, **Viral Immunology**, 32(2) 2019, 76-83.

Villenave R, Thavagnanam S, Sarlang S, Parker J, Douglas I, Skibinski G, Heane L. G, McKaigue J. P, Coyle P. V, Shields M. D, & Power U. F, *In Vitro Modeling of Respiratory Syncytial Virus Infection of Pediatric Bronchial Epithelium, the Primary Target of Infection in Vivo, Proceedings of the National Academy of Sciences of the United States of America*, 109(13), 2012, 5040–5045. https://doi.org/10.1073/PNAS.1110203109

Vianna L. A, Siqueira M. M, Volpini L. P, Louro I. D, & Resende P. C, *Seasonality, Molecular Epidemiology, and Virulence of Respiratory Syncytial Virus (RSV): A Perspective into the Brazilian Influenza Surveillance Program*, **Plos One,** 16(5), 2021, 0251361.

Von Hammerstein A. L, Aebi C, Barbey F, Berger C, Buettcher M, Casaulta C, & J. Trück J, *Interseasonal RSV Infections in Switzerland-Rapid Establishment of a Clinician-Led National Reporting System (RSV EpiCH),* **Swiss Medical Weekly,** 151, 2021, 30057.

Varela, Scotta F. H, Polese-Bonatto M. C, Sartor M, N Ferreira I. T. S, Fernandes C.F.I.R, & *COVID Study Group, Absence of Detection of RSV and Influenza During the COVID-19 Pandemic in a Brazilian Cohort: Likely Role of Lower Transmission in the Community*, **Journal of Global Health**, 2, 2021, 11.

Vijayan R, & Gourinath S, *Structure-Based Inhibitor Screening of Natural Products Against NSP15 of SARS-CoV-2 Revealed Thymopentin and Oleuropein as Potent Inhibitors*, **Journal of Proteins and Proteomics**, 12, 2021, 71-80.

Vittucci A. C, Piccioni L, Coltella L, Ciarlitto C, Antilici L, Bozzola E, & Villani A, *The Disappearance of Respiratory Viruses in Children During the COVID-19 Pandemic*, **International Journal of Environmental Research and Public Health,** 18(18), 2021, 9550.

Voermans J.J, Mulders D.G, Pas S.D, Koopmans M.P, van der Eijk A.A, & Molenkamp R, *Performance Evaluation of the Panther Fusion® Respiratory Tract Panel*, **Journal of Clinical Virology,** 123, 2020, 104232.

Welliver T. P, Garofalo R. P, Hosakote Y, Hintz K. H, Avendano L, Sanchez K, Velozo L, Jafri H, Chavez-Bueno S, Ogra P. L, McKinney L. A, Reed J. L, & Welliver R. C., *Severe Human Lower Respiratory Tract Illness Caused by Respiratory Syncytial Virus and Influenza Virus is Characterized by the Absence of Pulmonary Cytotoxic Lymphocyte Responses,* **Journal of Infectious Diseases**, 195(8), 2007, 1126–1136. https://doi.org/10.1086/512615

Wolters F, Grünberg M, Huber M, Kessler H. H, Prüller F, Saleh L, & Melchers W. J, *European Multicenter Evaluation of Xpert® and Xpress SARS-CoV-2/Flu/RSV Test*, **Journal of Medical Virology,** 93(10), 2021, 5798-5804.

Wagatsuma K, Koolhof I. S, Shobugawa Y, & Saito R, *Decreased Human Respiratory Syncytial Virus Activity during the COVID-19 Pandemic in Japan: An Ecological Time-Series Analysis,* **BMC Infectious Diseases,** 21, 2021, 1-13.

Wang J, Shi C, Xu Q, & Yin H, SARS-CoV-2 *Nucleocapsid Protein Undergoes Liquid–Liquid Phase Separation into Stress Granules Through its N-terminal Intrinsically Disordered Region*, **Cell Discovery,** *7*(1), 2021, 5.

Wang X.L, Madhi S.A You, *Global Burden of Respiratory Infections Associated with Seasonal Influenza in Chidren under 5 years in 2018: A Systematic Review and Modelling Study*, **Lancent Global Health**, 8(4), 2020, 497-510 doi.10.1016/S2214-109X (19)30545-5.

Wei C, Tolksdorf K, Hirve S, Schuler E, Zhang W, Haas W, & Buda S, "*Evaluation of Using ICD-10 Code Data for Respiratory Syncytial Virus Surveillance*," **Influenza and Other Respiratory Viruses**, 14,(6), 2020, 630-637.

Welliver R. C, Checchia P. A, Bauman J. H, Fernandes A. W, Mahadevia P. J, & Hall C. B, *Fatality Rates in Published Reports of RSV Hospitalizations Among High-Risk and Otherwise Healthy Children,* **Current Medical Research and Opinion**, 26(9), 2010, 2175–2181. https://doi.org/10.1185/03007995.2010.505126

Wen X, Mo S, Chen S, Yu G, Gao L, Chen S, & Liu E, *Pathogenic Difference of Respiratory Syncytial Virus Infection in Cotton Rats of Different Ages*, **Microbial Pathogenesis**, 137, 2019, 103749.

Wildenbeest J.G, *International Changes in Respiratory Syncytial Virus (RSV) Epidemiology during the COVID-19 Pandemic: Association with School Closures*, **Influenza and Other Respiratory Viruses,** 16(5), 2022, 926-936.

Wilkins D, Yuan Y, Chang Y, Aksyuk A.A, Núñez B.S, Wählby-Hamrén U, & Esser M.T, *Durability of Neutralizing RSV Antibodies Following Nirsevimab Administration and Elicitation of the Natural Immune Response to RSV Infection in Infants*, **Nature Medicine**, 2, 2023, 1-8.

Willem X.L, Antillon M, Bilcke J, Jit M, & Beutels P, *Health and Economic Burden of Respiratory Syncytial Virus (RSV) Disease and the Cost-Effectiveness of Potential Interventions Against RSV Among Children under 5 years in 72 Gavi-Eligible Countries*, **BMC Medicine,** 18, 2020, 1-16.

Williams T. C, Sinha I, Barr I. G, & Zambon M, *Transmission of Paediatric Respiratory Syncytial Virus and Influenza in the Wake of the COVID-19 Pandemic*, **Eurosurveillance,** 26(29), 2021, 2100186.

Wonodi C. B, Deloria-Knoll M, Feikin D. R, DeLuca A. N, Driscoll A. J, Moïsi J. C, Johnson H. L, Murdoch D. R, O'Brien K. L, Levine O. S, & Scott J. A. G, *Evaluation of Risk Factors for Severe Pneumonia in Children: The Pneumonia Etiology Research for Child Health Study,* **Clinical Infectious Diseases,** 54(2), 2012, 124–131. https://doi.org/10.1093/cid/cir1067

World Health Organization. Coronavirus (COVID19). https://who.sprinklr.com/. Accessed April 6, 2020.

World Health Organization. Coronavirus disease (COVID-19) Advice for the Public, 2020

.

Yeoh D. K, Foley D. A, Minney-Smith C. A, Martin A. C, Mace A. O, Sikazwe C. T, & Moore H. C, *Impact of Coronavirus Disease 2019 Public Health Measures on Detections of Influenza and Respiratory Syncytial Virus in Children during the 2020 Australian Winter,* **Clinical Infectious Diseases**, 72(12), 2021, 2199-2202.

Yu J.M, Fu Y.H, Peng X. L, Zheng Y. P, & He J. S, *Genetic Diversity and Molecular Evolution of Human Respiratory Syncytial Virus A and B*, **Scientific Reports,** 11(1), 2021**,** 12941.

Yun K. W, Choi E. H, & Lee H. J, *Molecular Epidemiology of Respiratory Syncytial Virus for 28 Consecutive Seasons (1990-2018) and Genetic Variability of the Duplication Region in the G gene of Genotypes ON1 and BA in South Korea*, **Archives of Virology,** 165(5), 2020**,** 1069-1077.

Yuan X, Hu T, He H, Qiu H, Wu X, Chen J, Wang M, Chen C, & Huang S., *Respiratory Syncytial Virus Prolifically Infects N2a Neuronal Cells, Leading to TLR4 and Nucleolin Protein Modulations and RSV F Protein Co-Localization with TLR4 and Nucleolin*, **Journal of Biomedical Science,** 25(1), 2018, 1. https://doi.org/10.1186/S12929-018-0416-6

Zel D, Toh Z. Q, Mulholland K, Pellicci D. G, & Licciardi P. V, *Severe Respiratory Syncytial Rus Disease in Preterm Infants: A Case of Innate Immaturity*, **Thorax**, 76(9), 2021 942-950.

Zhang S, Akmar L. Z, Bailey F, Rath B. A, Alchikh M, Schweiger B, & Nair H, *Cost of Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection Management in Young Children at the Regional and Global Level: A Systematic Review and Meta-Analysis*, **The Journal of Infectious Diseases**, 222(7), 2020, 680-687.

Zheng Z, Pitzer V. E, Shapiro E. D, Bont L. J, & Weinberger D. M, *Estimation of the Timing and Intensity of Reemergence of Respiratory Syncytial Virus Following the COVID-19 Pandemic in the US*, **JAMA Network Open**, 4(12), 2021, 2141779-2141779.

Zheng Z, Warren J. L, Shapiro E. D, Pitzer V. E, & Weinberger D. M, *Estimated Incidence of Respiratory Hospitalizations Attributable to RSV Infections Across Age and Socioeconomic Groups,* **Pneumonia**, 14(1), 2022, 1.

Zhu J, Miao Q, Tang J, Wang X, Dong D, Liu T, Qi R, Yang Z, Liu G, *Nucleolin Mediates the Internalization of Rabbit Hemorrhagic Disease Virus through Clathrin-Dependent Endocytosis*, **PLoS Pathog,** 14(10), 2018, 1007383.

Dissertation

Alnajjar S, *Therapeutic efficacy of antiviral compounds in the Neonatal lamb model of respiratory syncytial virus infection of infants with pathogenesis of secondary Streptococcus pneumoniae infection (***Doctoral dissertation, Iowa State University***) 2019.*

Online

NCDC. COVID-19 Nigeria-Nigeria Centre for Disease Control 2020.

Conference Proceeding

Simon A.K, Hollander G.A, & McMichael A, *Evolution of the immune system in humans from infancy to old age.* **Proceedings of the Royal Society B: Biological Sciences,** *282*(1821) 2015, 20143085.

Appendices

TELEGRAMS..... TELEPHONE.....

MINISTRY OF HEALTH
DEPARTMENT OF PLANNING, RESEARCH & STATISTICS DIVISION
PRIVATE MAIL BAG NO. 5027, OYO STATE OF NIGERIA

Your Ref. No. .....
All communications should be addressed to the Honorable Commissioner quoting
Our Ref. No. AD 13/479/43749B 30th MARCH, 2023

The Principal Investigator,
Lead City University,
Ibadan, Oyo State.
Nigeria.

Attention: AKINOLA ADEFUNKE IYABO

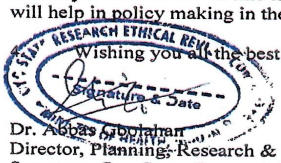
ETHICS APPROVAL FOR THE IMPLEMENTATION
OF YOUR RESEARCH PROPOSAL IN OYO STATE

This is to acknowledge that your Research Proposal titled: "**Prevalence of Respiratory Syncytial Virus (RSV) in Covid-19 Negative Older Adult and Children 5 Years and Below.**" has been reviewed by the Oyo State Ethics Review Committee.

2. The committee has noted your compliance. In the light of this, I am pleased to convey to you the full approval by the committee for the implementation of the Research Proposal in Oyo State, Nigeria.

3. Please note that the National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations, in line with this, the Committee will monitor closely and follow up the implementation of the research study. However, the Ministry of Health would like to have a copy of the results and conclusions of findings as this will help in policy making in the health sector.

4. Wishing you all the best.



Dr. Abbas Gbolahan
Director, Planning, Research & Statistics
Secretary, Oyo State, Research Ethics Review Committee

INSTITUTE FOR ADVANCED MEDICAL RESEARCH AND TRAINING (IAMRAT)
College of Medicine, University of Ibadan.
Director: Prof. IkeOluwapo O. Ajayi,
MBBS (Ib), M. CL.SC., MPH, Ph.D, MD, FMCGP, FWACP
Email: ioajayi@com.ui.edu.ng, ikeajayi2003@yahoo.com Tel: 08023268431

UI/UCH EC Registration Number: **NHREC/05/01/2008a**

NOTICE OF FULL APPROVAL AFTER FULL COMMITTEE REVIEW

Re: Prevalence of respiratory syncytial virus (RSV) in COVID-19 negative older adults and children 5years and below in Ibadan Southwest Nigeria

UI/UCH Ethics Committee assigned number: UI/EC/23/0607
Name of Principal Investigator: **Adefunke I. Akinola**
Address of Principal Investigator: Department of Biological Sciences
Lead City University, Ibadan

Date of receipt of valid application: 20/09/2023

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and *given full approval by the UI/UCH Ethics Committee.*

This approval dates from **06/10/2023 to 05/10/2024.** If there is delay in starting the research, please inform the UI/UCH Ethics Committee so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the* UI/UCH EC *assigned number and duration of* UI/UCH EC *approval of the study.* It is expected that you submit your annual report as well as an annual request for the project renewal to the UI/UCH EC at least four weeks before the expiration of this approval in order to avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the UI/UCH EC. *No changes are permitted in the research without prior approval by the* UI/UCH EC *except in circumstances outlined in the Code. The* UI/UCH EC *reserves the right to conduct compliance visit to your research site without previous notification.*

UI/UCH EC
06 OCT 2023
APPROVED
COLLEGE OF MEDICINE, U.I.

Dr O. S. Michael
For: Chairperson, UI/UCH Research Ethics Committee
E-mail: uiuchec@gmail.com

Bio-Data

A. Personal Data:

1.	**Full Name:**	Adefunke Iyabo AKINOLA Alapata Estate, Elewuro off Olorunda Aba Road, Akobo oju irin, Ibadan, Oyo State akinolaadefunke2013@gmail.com 08027202055/09061378327
2.	Date and Place of Birth:	29th March, 1972 Lagos State Nigeria
3.	Nationality:	Nigerian
4.	State of Origin:	Osun State
5.	Name and Address of Next of Kin:	Mr Akinola Olutunde Akintoye No 2, Alapata Estate, Elewuro off olrunda Aba Road Akobo Oju- irin Ibadan, Oyo State.

B. Educational Background:

1. Educational Institution Attended with Dates and Qualification:

School Attended	Dates	Qualification
❖ New State Primary School, Lagos,	1979-1984	First Leaving Sch. Cert.
❖ Oshodi Comprehensive High School Lagos	1985-1990	West African Exam. Cert.
❖ The School of Science Laboratory Technology, University of Ibadan	1991-1995	Ordinary Nat. Diploma
❖ The School of Science Laboratory Technology, University of Ibadam	1995-1998	Higher Nat. Diploma (Microbiology/Virology)
❖ Lead City University, Ibadan	2018-2020	PGD (General Microbiology)
❖ Lead City University, Ibadan	2020-2023	M. Sc. in View (Molecular Biology with Genomics)

2. Academic Qualifications obtained with (Dates)

Primary School Leaving Certificate	1984
West African Senior School Certificate WASCE	1990
Ordinary National Diploma	1995
Higher National Diploma	1998
Certificate of National service	1999
Post Graduate Diploma PGD	2020
Master of Science MSC in view	

3. Proessional Qualifications with Dates

Intermediate Diploma (OND) in Nigerian Institute of	
Science Laboratory Technology NISLT	1997
Japan International Coorperation Agency Certificate	2015
Cerificate of Paricipation in the group and	
Region Focused Training in Laboratory Diagnosis	
Techniques for the control of Vaccine	
Preventable Diseases Including Poliomyelitis and measlesat the	
National Instituteof infectious Diseases.	2015
Eorld Health Organization Certificate of the	
Polio Virus Cell Culture Refresher Course Training in	
Johannesburg, South Africa. .	2017
Associate member of NISLT	

C. Working Experiences with Dates:

Tutor with the Oyo State Teaching Service Commission (TESCOM), Oyo State.	2000-2012
Senior Technologist, Department of Virology,	
College of Medicine, University of Ibadan	2012 till date

D. **Awards and Fellowships (if any)** Aassociate Member of the Nigerian Institute of Science Laboratory Technology ((NISLT)

E. **Membership of Academic / Professional Bodies** Nigeria Inst. of Sci. Lab. Tech. (Associate)

F. **Publication**: Nil

G. **Major Conference Attended with Dates:**

Association of Science Laboratory Technologists of Nigeria, 2019 Technological Advancement towards Human Development: A Major Tool for Novel Research in the 21st Century.

3rd International Conference of the faculty of National and Applied Sciences

Nov 2nd-4th 2022:

Translational Research in Science for Sustainable Development Circa COVID-19 Era.

Association of Science Laboratory Technologist of Nigeria (ASLTON)@

8th-29th September 2022: Training on Leadership and Capacity Building.

H. **References**

1. Professor J. Ademiji

   08023009059

2. Dr. T.Y Raheem

   08097158720

_____ _____

Signature Date

Plagiarism Check Result

Akinola_Funke

ORIGINALITY REPORT

21%	23%	20%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	18%
2	maksimekin.github.io Internet Source	2%
3	www.intechopen.com Internet Source	2%

Exclude quotes	Off	Exclude matches	< 2%
Exclude bibliography	On		

The University Compliance Certification

This is to certify that this Thesis written by Adefunke Iyabo AKINOLA with Matric No. LCU/PG/000265 in the Department of Biological Science, Faculty of Natural and Applied Sciences, Lead City University, Ibadan is in full compliance with the approved University format and style.

_____ _____

Signature Date