DĄBROWSKA, Paulina, ŻUBER, Michał, BOCHYŃSKI, Karol, MOLENDA, Katarzyna, CIUBA, Katarzyna, BORODZIUK, Barbara, BORODZIUK, Filip, DACKA, Michał, GIŻEWSKA, Kamila and BIAŁOGŁOWSKI, Konrad. RSV Disease Threat and Innovative Prevention Methods in Health Protection: A Review. Journal of Education, Health and Sport. 2024;61:39-54. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.61.003
https://apcz.umk.pl/JEHS/article/view/48320
https://zenodo.org/records/10672406

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.01.2023. Revised: 08.02.2024. Accepted: 16.02.2024. Published: 16.02.2024.

RSV Disease Threat and Innovative Prevention Methods in Health Protection: A Review

Paulina Dąbrowska, Michał Żuber, Karol Bochyński, Katarzyna Molenda, Katarzyna Ciuba, Barbara Borodziuk, Filip Borodziuk, Michał Dacka, Kamila Giżewska, Konrad Białogłowski

Paulina Dąbrowska
paulina.dabrowska98@gmail.com
ORCID 0009-0004-6439-3357
Province Specialist Hospital named after Stefan Cardinal Wyszyński in Lublin
Al. Kraśnicka 100, 20-718 Lublin, Poland

Michał Żuber
michal.zuber10@gmail.com
ORCID: 0009-0000-2538-8556
4th Clinical University Hospital in Lublin,
ul. Kazimierza Jaczewskiego 8, 20-954 Lublin, Poland

Karol Bochyński
karolbochynski@gmail.com
ORCID 0009-0003-8309-2800
4th Clinical University Hospital in Lublin,
ul. Kazimierza Jaczewskiego 8, 20-954 Lublin, Poland
Katarzyna Molenda
zielinskakasia98@gmail.com
ORCID 0009-0005-1928-4220
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland
Katarzyna Ciuba
katarzyna.ciuba@onet.eu
ORCID 0009-0007-8347-3282
Province Specialist Hospital named after Stefan Cardinal Wyszyński in Lublinal.
Al. Kraśnicka 100, 20-718 Lublin, Poland

Barbara Borodziuk
basia.borodziuk@gmail.com
ORCID 0009-0009-2716-6653
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Filip Borodziuk
filipb899@gmail.com
ORCID 0009-0000-0394-1816
1 Military Clinical Hospital in Lublin,
al. Racławickie 23, 20-049 Lublin, Poland

Michał Dacka
michal.dackaa@gmail.com
ORCID 0009-0005-8783-6517
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Kamila Giżewska
gizewska.kamila@gmail.com
ORCID: 0000-0003-1682-180X
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Konrad Białogłowski
konrad.bialoglowski@gmail.com
ORCID: 0009-0001-1705-254X
University Clinical Hospital No. 1 in Lublin,
ul. Stanisława Staszica 16, 20-081 Lublin, Poland

ABSTRACT

Respiratory syncytial virus (RSV) causes infections of the lower respiratory tract. A group particularly vulnerable to severe infection are young children under 2 years of age and the elderly. The infection can cause the entire spectrum of respiratory symptoms from upper respiratory tract infections to severe courses requiring assisted breathing. Until recently, the only form of protection against infection was passive immunization, i.e. administration of immunoglobulins. Chief among these are palivizumab and nirsevimab. In May u June 2023, the Food and Drug Administration (FDA) approved for use 2 vaccines against RSV are Arexvy and Abrysvo. In this study, we focus on presenting and describing the clinical evidence supporting the effectiveness of these immunization methods.

Keywords: Respiratory syncytial virus (RSV), Bronchitis, RSV prevention, Palivizumab, Nirsevimab, RSV vaccine

1. Introduction

Respiratory syncytial virus (RSV) is one of the etiologic agents of inflammation of the lower respiratory tract. It is a particularly dangerous pathogen in the pediatric population under 2 years of age [1], 2], [3], but can infect and cause symptoms in people of all ages, being dangerous for older adults as well [4], [5]. It belongs to the Paramyxoviridae family, is a negatively polarized single-stranded RNA virus, has an envelope, and there are 2 RSV subtypes A and B [6]. First isolated in 1956, it is characterized by its ability to induce cell fusion, that is, to form syncytia- giant multinucleated cells. The virus uses two transmembrane glycoproteins, namely attachment glycoproteins (G) and fusion glycoproteins (F), to penetrate host cells. These glycoproteins play a key role in binding to the cell surface and facilitating fusion with cell membranes. RSV is transmitted by the droplet route, the incubation of the virus lasts 2-8 days, and the infectious period precedes the symptoms of the disease, so it spreads rapidly in the population. Incidence is seasonal. The virus is very common, with most children passing this infection by the age of two [7]. Passing the disease does not leave lasting immunity, so infection can occur up to several times during life [8].

2. Material and methods

The purpose of this study is to review and systematize the available data on passive and active immunization in the prevention of respiratory syncytial virus (RSV) disease. Based on sources available on the Internet, we reviewed the literature covering RSV-related topics. The results of searches in medical research databases PubMed, Google Scholar and Ebsco where the keywords used in the title or in the body were: "RSV", "bronchitis", "palivizumab", "nirsevimab", "RSV vaccine", "RSV prevention". We focused on full-text articles that covered issues related to RSV, the disease it causes and methods of prevention.

Keywords: „Respiratory syncytial virus (RSV)”, „Bronchitis”, „RSV prevention”, „Palivizumab”, „ Nirsevimab”, „RSV vaccine”.

3. Symptoms

RSV-induced disease covers a wide spectrum of respiratory symptoms. Clinical manifestations can range from the common cold and rhinitis to severe pneumonia [6]. Among the most common symptoms in children of all ages in highly developed countries are: Cough (90%), runny nose (61%), fever (59%), shortness of breath (57%), need for oxygen supplementation (27%), wheezing (27%), diarrhea (15%), need for Intensive Care Unit (ICU) admission (10%), pneumonia (3%), and need for mechanical ventilation (2%) [9].

In healthy children after the first year of life, acute RSV infection usually progresses with fairly mild symptoms such as cough, runny nose, fever and resolves within a few days after symptomatic treatment. In about one in three children under 12 months, acute bronchiolitis develops within 2-3 days. The cough changes its character becoming more intense, the work of the respiratory system increases, symptoms of dyspnea appear. Characteristic manifestations of the severe course are tachypnoe, nasal leakage, wheezing, hypoxemia and cyanosis. It is difficult to predict the evolution of acute bronchiolitis. The clinical condition of most children without chronic diseases with acute bronchitis from RSV infection improves within 3-4 days without hospitalization. Of those that required hospitalization, most improve with symptomatic treatment and can be discharged from the hospital within 2-3 days. One to three percent of infants under six months of age, especially those under two months of age and children with coexisting chronic diseases, may develop pulmonary complications. Thus, they require prolonged hospitalization, even admission to the pediatric or neonatal ICU for respiratory support and treatment of respiratory complications such as pneumonia, pneumothorax, and atelectasis [10].

3.1. RSV and asthma and wheezing

RSV infection may be associated with the onset of asthma or wheezing in later life [11], [12]. Severe primary RSV bronchiolitis in the first year of life is often followed by allergic asthma that persists into early adulthood. RSV patients with and without current asthma have reduced airway function as measured by spirometry [13]. Among the likely mechanisms explaining the chronic sequelae of RSV infection is the interaction between the subepithelial neuronal network of the airway mucosa and the cellular effectors of the inflammatory and immune response to the virus [14]. However, it is unclear whether this relationship is due to the direct effects and actions of RSV on the airways or whether it is a trigger for such symptoms in

predisposed children, and this topic requires further research [15]. Prevention of RSV infection may have a significant impact on preventing the occurrence of these complications.

3.2. Hospitalizations due to RSV

The incidence of RSV-related hospitalizations is 1-8% in the first year of life, meaning that one in 56 healthy term-born infants is hospitalized for RSV each year; in addition, children born in the fall had a higher risk of hospitalization than those born in other months [2].

3.3. RSV seasonality

Recent reports show that the COVID-19 pandemic has affected the seasonality of RSV in Australia. While no RSV cases were reported in the pediatric population during the 2020 winter season, these infections were reported in Australia and worldwide during the summer season. In 2022, the number of RSV cases in the state of New South Wales was about four times higher than in 2021. Similarly, large seasonal outbreaks of RSV were accompanied by increased hospitalizations in the northern hemisphere during the same period [16].

4. RSV prevention

Three strategies are currently being investigated in the prevention of RSV infection are: administering antibodies directly to the infant, acquiring antibodies through the placental route from a mother who has been vaccinated, and vaccinating children [17].

4.1. Monoclonal antibodies (mAbs)

4.1.1. Palivizumab

Palivizumab is a humanized monoclonal antibody belonging to the immunoglobulin class IgG1κ. Its action is directed against an epitope in the antigenic "A" site of the respiratory syncytial virus fusion protein. It exhibits potent virus neutralizing and fusion inhibitory activity. When administered to children at increased risk of infection, it reduces the incidence of hospitalization for RSV infection, but does not affect the severity of RSV infection. In their study, Schepp et al. showed clear efficacy in reducing the incidence of infection and thus reducing the number of hospitalizations for RSV infection, palivizumab prophylaxis significantly reduces the incidence of infection in premature infants (<32 weeks' gestation) [18]. Garegnani et al. in their study suggest that for a group of children at high risk of RSV infection due to comorbidities, palivizumab prophylaxis reduces hospitalizations for RSV infection, results in a small reduction in hospitalizations for respiratory-related illnesses, and may result in a significant reduction in RSV infections [19]. Research into an alternative form

of administration of palivizumab is also noteworthy. Intranasal administration appears to be an interesting alternative because it is less invasive and lower doses are used. However, daily intranasal administration of the antibody did not prevent RSV infection [20].

4.1.2. Nirsevimab

Nirsevimab is a recombinant human IgG1κ monoclonal antibody designed to target the pre-F protein of RSV virus. Its mechanism of infecting the cell is to penetrate cell membranes by changing the pre-fusion (pre-F) protein structure to a stable post-fusion (post-F) structure [21]. It is an approved drug for use in all infants [22]. Nirsevimab has a favorable safety profile, and the incidence of side effects is low and is comparable to placebo. The HARMONIE Study Group found the efficacy of nirsevimab in the context of hospitalization rates for RSV-related lower respiratory tract infection was 89.6% in France, 74.2% in Germany and 83.4% in the UK. [23]. The MELODY Study Group in its study showed that a single injection of nirsevimab given before the RSV season protected healthy preterm and term-born infants from RSV-related lower respiratory tract infection. At 150 days after injection, the efficacy in preventing hospitalization for RSV-related lower respiratory tract infection was 76.8%, and the efficacy in preventing very severe RSV-related lower respiratory tract infection was 78.6%. [24]. The study by Wilkins et al. analyzed serum samples from 2,143 infants included in the study to characterize baseline levels of RSV-specific immunoglobulin G antibodies and neutralizing antibodies (NAbs), the duration of RSV NAb levels after nirsevimab administration, the risk of RSV exposure during the first year of life, and the infant's adaptive immune response to RSV after nirsevimab administration. The study concluded that Nirsevimab provided sustained high levels of NAb throughout the infant's first RSV season and prevented RSV disease while allowing the development of an immune response to RSV [25].

4.2. RSV vaccination

In 2023, the world's first respiratory syncytial virus vaccines were approved in the US and Europe are Arexvy for people 60 years of age and older and Abrysvo, which was also approved for people 60 years of age and older and for pregnant women between 24 and 36 weeks of pregnancy. The road to this medical breakthrough has been long and challenging. The first attempts to create a vaccine were made in the 1960s. It was a formalin-inactivated vaccine, and its use was unsuccessful. The vaccine did not protect against infection, and

actually led to a pathological response to RSV, causing pneumonia and even death in two infants. [26], [27].

The ideal vaccine should protect against the disease and reduce RSV transmission. Various types of vaccines have been studied over the years and include mRNA, subunit and particle-based vaccines, live attenuated or chimeric vaccines, and vaccines based on recombinant vectors [28]. For the best protection of newborns, the most effective method seems to be the one combining passive and active immunization. This strategy could be implemented by vaccinating the mother while she is still pregnant, so that the antibodies she produces will be transported to the fetus and protect the newborn during the first months of life, followed by active immunization of children directly with the vaccine. [29]. In this paper, we will focus on describing two approved vaccines.

4.2.1. AREXVY

AREXVY consists of an RSVPreF3 antigen component, i.e., 120 µg of recombinant RSV surface glycoprotein F from an RSV-A strain that is stabilized in the pre-fusion trimeric conformation, and an AS01E adjuvant component (RSV F protein is the main surface virus antigen, well-conserved across RSV-A and -B subtypes). AREXVY is administered intramuscularly (IM) as a single (0.5 mL) dose [30]. Below we will describe the course and conclusions of some of the vaccine's clinical trials.

The phase 1 clinical trial being conducted in the US and Belgium starting in 2019 enrolled 48 subjects aged 18-40 and 1005 subjects aged 60-80. Participants were randomized into equally sized groups to receive 2 doses of unadjuvanted (YAs and OAs) or AS01-adjuvanted (OAs) vaccine or placebo 2 months apart. The study evaluated the safety and immunogenicity of each variant. Side effects were mostly transient of mild to moderate degree. The RSVPreF3 vaccines boosted humoral responses: RSVPreF3-specific immunoglobulin G and RSV-A neutralizing antibody. This effect persisted throughout the observation period. Based on safety and immunogenicity profiles, the AS01E-adjuvanted vaccine containing 120 µg of RSVPreF3 was selected for further clinical development [31]. A phase 2 clinical trial was then conducted, which included 122 adults aged 60-80 years who had participated in the previous study. They were given subsequent doses of the vaccine to further evaluate safety and immunogenicity. The safety of the vaccine after a 6-month follow-up was found to be similar to that of the phase 1 study, and no serious adverse events or potential immunological disorders were observed. Neutralizing titers and cell-mediated immune responses persisted for 18 months

after 2-dose vaccination. Dose 3 increased RSV-specific neutralizing titers against RSV-A and RSV-B and median CD4+ T-cell frequencies. Based on these results, it was concluded that vaccination 18 months after the second dose is well tolerated and immunogenic in older patients [32].

Subsequently, several phase 3 clinical trials were conducted. The study groups included people over 50 years old.

The randomized study by Schwarz et al. conducted in various countries around the world, with a follow-up time of 3 years, qualified participants were at least 60 years old. The safety and reactogenicity of the vaccine were evaluated as in previous studies. The most common local side effect was injection site pain in 60.5% of participants, while systemic side effects were muscle aches in 33.5% and fatigue in 31.4%. Most side effects were transient and lasted about 2 days, and were mild to moderate in severity. One case of vaccine-associated Guillain-Barre syndrome was identified [33].

Another clinical trial enrolled 24966 participants who were at least 60 years old, and primarily tested its efficacy. They received a single dose of the study vaccine based on RSV prefusion F protein with adjuvant AS01E (RSVPreF3 OA) or placebo before the RSV season. Vaccine efficacy against RT-PCR-confirmed RSV-related lower respiratory tract disease was 82.6% (96.95% confidence interval [CI], 57.9 to 94.1), with 7 cases (1.0 per 1000 participant-years) in the vaccine group and 40 cases (5.8 per 1000 participant-years) in the placebo group. Vaccine efficacy was 94.1% (95% CI, 62.4 to 99.9) against severe RSV-related lower respiratory tract disease (assessed on the basis of clinical signs or by the investigator) and 71.7% (95% CI, 56.2 to 82.3) against RSV-related acute respiratory infection. Vaccine efficacy was similar against the RSV A and B subtypes (for RSV-related lower respiratory tract disease: 84.6% and 80.9%, respectively; for RSV-related acute respiratory infection: 71.9% and 70.6%, respectively). A single dose of RSVPreF3 OA vaccine had an acceptable safety profile and prevented RSV-related acute respiratory infections and lower respiratory tract disease, as well as severe RSV-related lower respiratory tract disease in adults aged 60 years or older, regardless of RSV subtype and the presence of comorbidities. [34].

4.2.2. ABRYSVO

ABRYSVO is a vaccine designed for: Actively immunizing pregnant individuals during the 32nd to 36th week of gestation to prevent lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus in infants from birth through 6 months of age.

Additionally, it is indicated for active immunization to prevent LRTD caused by RSV in individuals aged 60 years and older [35]. The antigen component contains recombinant RSV preF A and RSV preF B. The RSV preF A and RSV preF B recombinant proteins are expressed in genetically engineered Chinese Hamster Ovary cell lines grown in suspension culture using chemically-defined media, without antibiotics oranimal-derived components. The recombinant proteins are purified through a series of column chromatographyand filtration steps followed by formulation, filling into vials, and lyophilization. After reconstitution, each dose of ABRYSVO is approximately 0.5 mL [35]. Below we will present the course and conclusions of some of the clinical trials of this vaccine.

The randomized placebo-controlled clinical trial Falsey et al. launched in 2018 involved 2 groups of patients divided by age criteria: 18-49 years and 50-85 years. Its aim was to evaluate the safety, tolerability and immunogenicity of RSV vaccines Participants received 60, 120, or 240 μg of RSVpreF (with or without aluminum hydroxide) alone or concomitantly with seasonal inactivated influenza vaccine (SIIV). Concomitant administration with SIIV did not affect safety among younger or older adults. All RSVpreF formulations with or without concomitant SIIV elicited strong RSV-neutralizing serum responses in adults aged 50-85 years 1 month after vaccination. RSVpreF formulations administered alone or with SIIV were well tolerated and highly immunogenic in older adults, confirming the potential of RSVpreF to protect older adults from RSV disease. [36]

The phase 2b clinical trial evaluated the safety and immunogenicity of simultaneous injection of stabilized RSV subunit vaccine (RSVpreF) and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) to healthy, non-pregnant women aged 18-49 years. Based on the study, it was assessed that the study vaccines were safe and well tolerated also when given together with the Tdap vaccine. The research demonstrated that the immune responses to the tetanus and diphtheria components of Tdap, when given simultaneously with RSVpreF, were not inferior to the immune responses generated by Tdap alone. Similarly, the study showed that the neutralizing responses against RSV-A and RSV-B induced by RSVpreF, when administered concurrently with Tdap, were not inferior to the responses elicited by RSVpreF alone. Following vaccination, all vaccine groups exhibited a significant rise in antibody responses against pertussis antigen. However, it's important to note that the responses to the pertussis components of Tdap did not meet the pre-established noninferiority criteria when Tdap was administered concomitantly with RSVpreF, as compared to the administration of Tdap alone [37].

The phase 2a study involved adults aged 18-50, divided into two equal groups for either placebo or a single intramuscular injection of the RSVpreF. Around 28 days post-injection, individuals received intranasal inoculation with the RSV A Memphis 37b challenge virus and were monitored for a period of 12 days. Following the administration of the challenge virus, the vaccine demonstrated an efficacy of 86.7% (95% CI, 53.8 to 96.5) in preventing symptomatic RSV infection, confirmed by the presence of any detectable viral RNA on at least 2 consecutive days. In addition, the study evaluated the safety of the vaccine, concluded that RSVpreF was safe and no serious adverse reactions were observed. 38]

The vaccine was also tested for safety and immunogenicity on a group of pregnant women between 24-36 weeks' gestation. The incidence of adverse events in women and infants was similar in the vaccine and placebo groups, and the type and frequency of these events were consistent with the incidence among pregnant women and infants. [39].

This was followed by a phase 3 clinical trial involving pregnant women 40]. Pregnant women at 24-36 weeks' gestation were divided 1:1 to receive a single intramuscular injection of 120 μg of RSVpreF or placebo. The main effectiveness measures included severe lower respiratory tract illness associated with RSV that required medical attention, as well as RSV-related lower respiratory tract illness requiring medical attention in infants within 90, 120, 150, and 180 days post-delivery. The RSVpreF vaccine, when administered during pregnancy, demonstrated efficacy in preventing medically attended severe lower respiratory tract illness associated with RSV in infants, and no safety issues were observed [41].

A phase 3 trial assessed the RSVpreF vaccine's efficacy and safety in adults aged 60 and above, targeting RSV infections. Participants received a single 120 μg intramuscular injection of RSVpreF vaccine or a placebo in a 1:1 ratio. Interim analysis included 34,284 participants. Vaccine efficacy: 66.7% against RSV-associated lower respiratory tract illness with at least two symptoms, 85.7% against RSV-associated lower respiratory tract illness with at least three symptoms, 62.1% against RSV-associated acute respiratory illness. Local reactions were more common with the vaccine (12%) than the placebo (7%), systemic events were similar (27% vs. 26%). Comparable rates of adverse events (9.0% vaccine, 8.5% placebo) within one month post-injection. Severe adverse events reported in 0.5% of vaccine recipients and 0.4% of placebo recipients. There were no apparent safety concerns, and serious adverse events occurred with a frequency of 2.3% in both groups. Based on the study, it was concluded that the RSVpreF vaccine is effective in preventing RSV-related respiratory disease in adults aged 60 years and older [42].

5. Summary

RSV represents a significant public health challenge, especially in the context of infants and the elderly. The introduction of preventive strategies and effective vaccines against RSV is undoubtedly a breakthrough that reduces complications and costs associated with hospitalization and treatment. Due to the recently noted change in RSV prevalence by both season and age group, it is unclear how the virus will evolve in the future. palivizumab and nirsevimab, as representatives of passive immunization, show the ability to significantly reduce the risk of RSV infection, especially in at-risk groups such as premature infants and children with chronic diseases. Based on the sources analyzed, available vaccination for the elderly has been shown to be safe and effective in preventing infection. Vaccination of pregnant women protects the most vulnerable population that RSV hits with particular intensity, namely premature and newborn babies. However, whether this protection will be effective in the context of older children, in the age group up to 24 months, where the virus is particularly dangerous we do not know. The most interesting question we are left with after this literature review is: Will it be possible to develop a safe and highly immunogenic vaccine for use in the pediatric population? Research in this area is still developing, and dozens of new vaccine candidates are being studied.

Disclosure

Authors contribution:

Conceptualization: Paulina Dąbrowska, Michał Żuber, Katarzyna Molenda, Karol Bochyński

Methodology: Paulina Dąbrowska, Michał Żuber, Katarzyna Ciuba, Barbara Borodziuk

Formal Analysis: Michał Dacka, Konrad Białogłowski, Karol Bochyński, Kamila Giżewska

Investigation: Michał Żuber, Paulina Dąbrowska, Katarzyna Molenda, Barbara Borodziuk

Writing – Rough Preparation: Paulina Dąbrowska, Michał Dacka, Karol Bochyński, Katarzyna Ciuba

Writing – Review and Editing: Michał Żuber, Konrad Białogłowski, Filip Borodziuk, Kamila Giżewska

Visualization: Michał Dacka, Katarzyna Molenda, Katarzyna Ciuba, Michał Żuber, Filip Borodziuk

All authors have read and agreed with the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Funding statement: No external funding was received to perform this review.

Board statement: Not applicable – this review included analysis of the available literature.

Statement of informed consent: not applicable.

References

1. Simoes EA. Respiratory syncytial virus infection. Lancet. 1999;354(9181):847-852. doi:10.1016/s0140-6736(99)80040-3.
2. Wildenbeest JG, Billard MN, Zuurbier RP, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. Lancet Respir Med. 2022. doi:10.1016/s2213-2600(22)00414-3.
3. Jain S, Williams DJ, Arnold SR, et al. Community-Acquired pneumonia requiring hospitalization among U.S. children. New Engl J Med. 2015;372(9):835-845. doi:10.1056/nejmoa1405870.
4. Dowell SF, Anderson LJ, Gary HE, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. J Infect Dis. 1996;174(3):456-462. doi:10.1093/infdis/174.3.456
5. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. J Infect Dis. 2012;206(1):56-62. doi:10.1093/infdis/jis309.
6. Collins PL, Fearns R, Graham BS. Respiratory syncytial virus: virology, reverse genetics, and pathogenesis of disease. Curr Top Microbiol Immunol. 2013;372:3-38. doi:10.1007/978-3-642-38919-1_1
7. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child. 1986;140(6):543-546. doi:10.1001/archpedi.1986.02140200053026
8. Fuentes S, Coyle EM, Beeler J, Golding H, Khurana S. Antigenic fingerprinting following primary RSV infection in young children identifies novel antigenic sites and reveals unlinked evolution of human antibody repertoires to fusion and attachment glycoproteins. PLOS Pathog. 2016;12(4):e1005554. doi:10.1371/journal.ppat.1005554.

9. Jiang MY, Duan YP, Tong XL, et al. Clinical manifestations of respiratory syncytial virus infection and the risk of wheezing and recurrent wheezing illness: a systematic review and meta-analysis. World J Pediatr. 2023. doi:10.1007/s12519-023-00743-5.
10. Sawyer MH, Barnett E, Lynfield R, Kimberlin DW. Red Book 2021: Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2021.
11. Marlow R, Finn A, Henderson J. Assessing the association between bronchiolitis in infancy and recurrent wheeze: a whole English birth cohort case–control study. Thorax. 2019;74(5):503-505. doi:10.1136/thoraxjnl-2018-212203.
12. Simões EA, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick L, Groothuis JR. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. J Allergy Clin Immunol. 2010;126(2):256-262. doi:10.1016/j.jaci.2010.05.026.
13. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax. 2010;65(12):1045-1052. doi:10.1136/thx.2009.121582.
14. Piedimonte G. Pathophysiological mechanisms for the respiratory syncytial virus-reactive airway disease link. Respir Res. 2002;3(S1). doi:10.1186/rr185.
15. Fauroux B, Simões EA, Checchia PA, et al. The burden and long-term respiratory morbidity associated with respiratory syncytial virus infection in early childhood. Infect Dis Ther. 2017;6(2):173-197. doi:10.1007/s40121-017-0151-4.
16. Walker GJ, Foster CS, Sevendal A, et al. Clinical, genomic, and immunological characterization of RSV surge in sydney, australia, 2022. Pediatrics. 2024. doi:10.1542/peds.2023-063667.
17. Iofrío de Arce A, Álvarez García FJ. Nirsevimab and other strategies for the prevention of RSV infection. An Pediatr (Engl Ed). 2023. doi:10.1016/j.anpede.2023.09.007.
18. Schepp RM, Kaczorowska J, van Gageldonk PG, et al. Effect of palivizumab prophylaxis on respiratory syncytial virus infection in very preterm infants in the first year of life in the netherlands. Vaccines. 2023;11(12):1807. doi:10.3390/vaccines11121807.
19. Garegnani L, Roson Rodriguez P, Escobar Liquitay CM, Esteban I, Franco JV. Palivizumab for preventing respiratory syncytial virus (RSV) infection in children. Cochrane Database Syst Rev. 2020. doi:10.1002/14651858.cd013757.

20. Mazur NI, Löwensteyn YN, Terstappen J, et al. Daily intranasal palivizumab to prevent respiratory syncytial virus infection in healthy preterm infants: a phase 1/2b randomized placebo-controlled trial. eClinicalMedicine. 2023;66:102324. doi:10.1016/j.eclinm.2023.102324.
21. Boyoglu-Barnum S, Chirkova T, Anderson LJ. Biology of Infection and Disease Pathogenesis to Guide RSV Vaccine Development. Front Immunol. 2019;10. doi:10.3389/fimmu.2019.01675.
22. Keam SJ. Nirsevimab: First Approval. Drugs. 2022. doi:10.1007/s40265-022-01829-6.
23. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. New Engl J Med. 2023;389(26):2425-2435. doi:10.1056/nejmoa2309189.
24. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. New Engl J Med. 2022;386(9):837-846. doi:10.1056/nejmoa21102755.
25. Wilkins D, Yuan Y, Chang Y, et al. Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants. Nat Med. 2023. doi:10.1038/s41591-023-02316-5.
26. Venkatesan P. First RSV vaccine approvals. Lancet Microbe. 2023. doi:10.1016/s2666-5247(23)00195-7.
27. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (rs) virus infection in children previously vaccinated with an inactivated rs virus vaccine. Am J Epidemiology. 1969;89(4):405-421. doi:10.1093/oxfordjournals.aje.a120954.
28. Topalidou X, Kalergis AM, Papazisis G. Respiratory Syncytial Virus Vaccines: A Review of the Candidates and the Approved Vaccines. Pathogens. 2023;12(10):1259. doi:10.3390/pathogens12101259.
29. Mejias A, Rodríguez-Fernández R, Oliva S, Peeples ME, Ramilo O. The journey to a respiratory syncytial virus vaccine. Ann Allergy Asthma Amp Immunol. 2020;125(1):36-46. doi:10.1016/j.anai.2020.03.017.
30. U.S. Food and Drug Administration. Accessed January 15, 2024. https://www.fda.gov/media/168519/download. [(accessed on 15.01.2024)]
31. Leroux-Roels I, Davis MG, Steenackers K, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older

Adults: Phase 1/2 Randomized Clinical Trial. J Infect Dis. 2023;227(6):761-772. doi:10.1093/infdis/jiac327.

32. Leroux-Roels I, Van Ranst M, Vandermeulen C, et al. Safety and Immunogenicity of a Revaccination With a Respiratory Syncytial Virus Prefusion F Vaccine in Older Adults: A Phase 2b Study. J Infect Dis. Published online September 12, 2023. doi:10.1093/infdis/jiad321.
33. Schwarz TF, Hwang SJ, Ylisastigui PP, et al. 119. Safety and Reactogenicity of an Investigational Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine for Adults ≥ 60 Years of Age (RSVPreF3 OA): an Interim Analysis at 6 Months after Vaccination. Open Forum Infect Dis. 2022;9(Supplement_2). doi:10.1093/ofid/ofac492.197.
34. Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. New Engl J Med. 2023;388(7):595-608. doi:10.1056/nejmoa2209604.
35. ABRYSVO. U.S. Food and Drug Administration. Accessed January 20, 2024. http://www.fda.gov/vaccines-blood-biologics/abrysvo
36. Falsey AR, Walsh EE, Scott DA, et al. Phase 1/2 Randomized Study of the Immunogenicity, Safety, and Tolerability of a Respiratory Syncytial Virus Prefusion F Vaccine in Adults With Concomitant Inactivated Influenza Vaccine. J Infect Dis. 2021. doi:10.1093/infdis/jiab611.
37. Peterson JT, Zareba AM, Fitz-Patrick D, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F Vaccine When Coadministered With a Tetanus, Diphtheria, and Acellular Pertussis Vaccine. J Infect Dis. 2021. doi:10.1093/infdis/jiab505.
38. Schmoele-Thoma B, Zareba AM, Jiang Q, et al. Vaccine Efficacy in Adults in a Respiratory Syncytial Virus Challenge Study. New Engl J Med. 2022;386(25):2377-2386. doi:10.1056/nejmoa2116154.
39. Simões EA, Center KJ, Tita AT, et al. Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy. New Engl J Med. 2022;386(17):1615-1626. doi:10.1056/nejmoa2106062.
40. Pfizer Announces Positive Top-Line Data of Phase 3 Global Maternal Immunization Trial for its Bivalent Respiratory Syncytial Virus (RSV) Vaccine Candidate. Pfizer. Accessed January 21, 2024. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global

41. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. New Engl J Med. 2023. doi:10.1056/nejmoa2216480.
42. Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. New Engl J Med. 2023. doi:10.1056/nejmoa2213836