**DOI:** 10.5578/ced.20240410 • *J Pediatr Inf 2024;18(4):e262-e266*

# Questions on Immunization and Vaccination and Short Answers

## Bağışıklama ve Aşı ile İlgili Sorular ve Kısa Cevaplar

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**Cite this article as:** Coşkun A, Kara A. Questions on immunization and vaccination and short answers. J Pediatr Inf 2024;18(4):e262-e266.

At the last meeting of the World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE) on 23-26 September 2024, given the global burden of severe lower respiratory tract infection due to respiratory syncytial virus (RSV), it was recommended that all countries introduce passive immunization to prevent RSV disease in early infancy. SAGE also emphasized that RSV is a major cause of morbidity and mortality in older adults.

This article provides short answers to some frequently asked questions about RSV vaccines and monoclonal antibodies against RSV.

**Question 1: What are the characteristics of RSV vaccines and monoclonal antibodies?**

Respiratory syncytial virus, which is an RNA virus belonging to the genus Pneumovirus of the Paramyxoviridae family, consists of 15.222 nucleotides encoding three transmembrane surface proteins (F, G, SH), two matrix proteins (M, M2) and three nucleocapsid proteins (N, P, L) and two non-structural proteins (NS1, NS2).

Among these, only surface fusion (F) and attachment (G) glycoproteins are important target proteins for vaccine development as they can stimulate RSV neutralizing antibody formation. The F protein, which forms a trimer structure by combining two subunits, F1 and F2, linked to each other by disulfide bonds, together with the G and SH proteins, is responsible for the fusion of the viral envelope to the host cell membrane and the formation of RSV-specific syncytium in cell culture. The F glycoprotein is highly unstable; it exists on the cell surface in two structures: Pre-fusion (pre-F) and post-fusion (post-F). Triggering the pre-F structure results in fusion of the virus and cell membranes and infection. When the F protein changes to the more stable post-F inactive structure, it cannot fuse with the cell membrane. In adult human sera, neutralizing activity is directed against the pre-fusion form of RSV. Therefore, the historical challenge in vaccine development has been due to the unstable nature of the pre-F structure. It was only when the F protein was able to lock onto the pre-F structure that an effective vaccine was finally developed.

While the genome of the F protein is still largely conserved, the G protein, which is responsible for RSV binding to the host cell, is more antigenically variable, making the development of a vaccine against the G protein even more challenging.

The types of RSV vaccines currently in phase studies can be classified into three groups: Live attenuated vaccines, chimeric vaccines (e.g. parainfluenza virus type 5-PIV5 vector vaccines), protein/peptide-based vaccines (subunit vaccines for F and G protein or synthetic virus-like particle vaccines), nucleic acid vaccines (RNA or mRNA vaccines).

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**Received:** 28.09.2024 **Accepted:** 25.11.2024 **Available Online Date:** 13.12.2024

Studies on combined RSV vaccines (with influenza, severe acute respiratory syndrome coronavirus-2 or human metapneumovirus) are also ongoing in phase I-II.

Other monoclonal antibodies (RSV mAb) being developed for immune prophylaxis also target the pre-F structure of the F protein of RSV virus.

**Question 2: What are the approved vaccines and monoclonal antibodies for RSV?**

Arexvy® (GSK) and Abrysvo® (Pfizer) are recombinant subunit protein vaccines containing a preF form of the spike protein found on the surface of RSV virus.

mResvia® (Moderna) is an mRNA vaccine that contains the mRNA encoding the pre-F form of the F glycoprotein of the RSV virus. This vaccine enables the immune system to produce and respond to antibodies by temporarily inducing the immunized person's own cells to produce the pre-F form of the spike protein. It is approved for use in the United States (May 2024), the European Union (August 2024) and Canada (November 2024).

Among these vaccines, the only vaccine that contains an adjuvant is the Arexvy® vaccine, which contains the AS01 adjuvant, a liposome-based system of two immune stimulants.

None of the currently approved RSV vaccines contain live virus and therefore do not cause RSV disease.

Palivizumab (Synagis®) (AstraZeneca) is a monoclonal antibody produced by recombinant DNA in mammalian cells that neutralizes a single domain (A) epitope found on both pre-F and post-F proteins and has been licensed in high-income countries since 1998.

Nirsevimab (Beyfortus®) (Sanofi), a mammalian cell-derived recombinant long acting antibody against the pre-fusion structure of the F glycoprotein of the RSV virus, is approved for use in the European Union (2022), United Kingdom (2022), Canada (2023) and United States (2023) for the prevention of RSV-associated severe lower respiratory tract infection in newborns during the first RSV season following birth.

**Question 3: What are the target groups for approved vaccines and monoclonal antibodies for RSV?**

For infants, there are two prevention approaches based on passive immunity: Maternal vaccination and monoclonal antibody administration to infants.

- There is only one vaccine (Abrysvo®) that has been licensed for maternal RSV vaccination (although there are differences between countries; it is recommended to be administered from 22 weeks to 36 weeks of gestational age).
- The monoclonal antibodies against RSV, nirsevimab (Beyfortus®) and palivizumab (Synagis®), are approved for the prevention of RSV-associated lower respiratory tract infection in newborns and early infancy during the first RSV season following birth.

For people aged 75 years and older; there are three approved RSV vaccines. These are Arexvy®, Abrysvo® and mResvia®.

For people aged 60-74 years; there are three RSV vaccines approved for people at risk for RSV-related lower respiratory tract infection. These are Arexvy®, Abrysvo® and mResvia®. All three vaccines are licensed in the United States (2023-2024), Canada (2023-2024) and the European Union (2023-2024).

For people under 60 years of age; there are two vaccines approved for different age groups for people at risk of RSV-related lower respiratory tract infection:

- Arexvy® has also been licensed in Europe (2024) and the United States (2024) for use in people aged 50-59 years who are at risk of RSV-related lower respiratory tract infection. However, the scheme of administration for this age group has not yet been determined.
- Abrysvo® has recently (October 2024) been approved by the US Food and Drug Administration for people aged 18-59 years who are at risk of RSV-related lower respiratory tract infection, with an expansion of the indication age group.

Market approved RSV vaccines (Arexvy®, Abrysvo®, mResvia®) and monoclonal antibody (Beyfortus®) have not yet been licensed in Türkiye.

**Question 4: What are the schemes and routes of administration for the approved vaccines and monoclonal antibodies for RSV?**

Maternal Immunization: At the last SAGE meeting, it was recommended that a single dose of maternal vaccination in the third trimester of pregnancy at a time interval defined by countries. Maternal antibodies produced by maternal vaccination provide protection for the newborn for approximately 5-6 months. Repeating maternal vaccination in every pregnancy is not currently recommended. However, as the vaccine becomes widely available, this information may change as repeated dosing data become available. Instead, it is recommended that a woman who was vaccinated in a previous pregnancy should ensure that her baby receives postnatal monoclonal antibody in the next pregnancy.

The Abrysvo® vaccine is recommended by the United States and Pan American Health Organization to be administered between the 32$^{nd}$ and 36$^{th}$ weeks of pregnancy, by the United Kingdom from the 28$^{th}$ week of pregnancy (indicating

that it can be administered from the 22nd week) until birth, and in Europe between the 22nd and 36th weeks of pregnancy with a dose of 0.5 ml for today.

**RSV monoclonal antibodies:** It is recommended to be administered to all newborns and all infants under eight months of age before the first RSV season, regardless of whether the mother was vaccinated during pregnancy. It is also recommended to be administered to infants aged 8-19 months in defined risk groups before the second RSV season.

- Palivizumab (Synagis®): It is a clear or slightly opaque liquid. It is administered into the anterolateral aspect of the vastus lateralis muscle (I.M.) in the middle or upper 1/3 of the thigh. It is available in 50 mg (0.5 ml) or 100 mg (1.0 ml) vials as two different doses. The recommended administration dose is 15 mg/kg. If the first dose is administered at the beginning of the RSV season, it is administered five times during the season, one dose per month. It should be stored between (+2) and (+8) °C under standard cold chain conditions. There are some data supporting that it can remain stable for at least eight hours at room temperature.
- Nirsevimab (Beyfortus®): It is a colorless/yellowish solution. It is administered into the anterolateral aspect of the vastus lateralis muscle (I.M.) in the middle or upper 1/3 of the thigh. It is available as a sterile liquid in ready-to-use syringes in two different doses of 50 mg (0.5 ml) or 100 mg (1.0 ml). It is administered at a dose of 50 mg (0.5 ml) to infants weighing less than five kilograms and 100 mg (1.0 ml) to infants weighing ≥5 kg. It is administered at a dose of 200 mg to infants between the ages of 8-19 months who are among defined risk groups. It should not be shaken. It should never be frozen. It should be stored between (+2) and (+8) °C under standard cold chain conditions. After removal from the refrigerator, it can remain stable at room temperature for up to eight hours. However, it should not be returned to the refrigerator after this period and should be discarded.

Arexvy®, Abrysvo® and mResvia® vaccines, approved for people aged 75 years and older and for people aged 60-74 years who are at risk of severe RSV disease, are currently recommended to be administered as one dose (0.5 ml). There is limited data on the best time for vaccination, with the best time reported to be before the start of the RSV season. Further evaluation is needed for countries where this season is unknown or where seasonality is variable.

Administration guidelines for risk groups under the age of sixty have not yet been published.

Details on vaccines and administration are presented below:

- Abrysvo® Vaccine: It is administered 0.5 ml intramuscularly (I.M.) into the deltoid muscle area of the upper arm. The lyophilized (freeze-dried) single-dose antigen compound is available in a vial and the reconstituent in a ready-to-use syringe. Single-dose/multidose vial presentation is still under development. The vaccine should be stored under standard cold chain conditions between (+2) and (+8) °C. It should never be frozen. It should be protected from light. Once reconstituted, it should never be frozen or refrigerated; it should be stored at room temperature between (+15) and (+30) °C. After reconstitution, it should preferably be used immediately, within four hours at the latest.
- Arexvy® Vaccine: 0.5 ml is administered intramuscularly (I.M.) into the deltoid muscle area of the upper arm. The lyophilized (freeze-dried) single-dose antigen component is presented in a vial, and the diluted adjuvant suspension component is presented in a separate vial without injector. The vaccine should be stored under standard cold chain conditions between (+2) and (+8) °C. It should never be frozen. It must be protected from light. After reconstitution, it should never be frozen; it should be stored in the refrigerator between (+2) and (+8) °C or at room temperature between (+15) and (+30) °C. After reconstitution, it should be protected from light and should preferably be used immediately after reconstitution, preferably within four hours at the latest.
- mResvia® Vaccine: 0.5 ml is administered intramuscularly (I.M.) into the deltoid muscle area of the upper arm. It is supplied in a ready-to-use single-dose (0.5 ml) syringe containing liquid in the form of a slightly grayish-white solution. As with any mRNA vaccine, it must not be shaken. The vaccine can be stored at (-40) to (-15) °C for one year. Once the vaccine in the syringe has thawed, it must not be refrozen. The vaccine can be stored between (+2) and (+8) °C for 30 days, protected from light. After removal from the refrigerator, it can be kept at room temperature between (+8) and (+25) °C for 24 hours, protected from light. However, it should not be returned to the refrigerator after this period and should be discarded.

**Question 5: What are the adverse events reported following approved vaccines for RSV?**

The most commonly reported adverse events following RSV vaccination are pain, redness, swellingat the site of vaccine administration, and fatigue, fever, headache, nausea, diarrhea, muscle and joint pain.

No serious adverse events were detected among vaccinated pregnant women. However, there was an increase in preterm births in the vaccinated group, although this was not statistically significant. This increase was observed particularly in clinical trial centers located in upper-middle-income countries. SAGE has recommended that maternal vaccination should be administered in the last trimester of pregnancy and that the interval of administration should be as narrow as possible to mitigate a possible risk of preterm birth.

However, cases of high blood pressure, including pre-eclampsia, have been reported in vaccinated pregnant women.

In some older adults, serious neurological conditions, including Guillain-Barre syndrome (GBS), have been reported following administration of protein-based RSV vaccines. Therefore, an increased risk of GBS following RSV vaccination (5-10 per million doses) is currently reported for people over 60 years of age.

The most commonly reported adverse effect following administration of nirsevimab (Beyfortus®) was rash within the first 14 days after administration. Other undesirable effects were pyrexia and injection site reactions.

The most commonly reported adverse events after palivizumab (Synagis®) administration are fever, rash and injection site reactions. The most serious adverse adverse event reported following palivizumab was anaphylaxis and other hypersensitivity reactions.

**Question 6: What are the contraindications and precautions for RSV vaccines and monoclonal antibodies?**

The absolute contraindication for RSV vaccination is a history of anaphylactic reaction to a previous dose of the vaccine or to any of its ingredients.

History of anaphylactic reaction following administration of RSV monoclonal antibodies, nirsevimab, palizumab or any other human monoclonal antibody, or to any of the ingredients of these antibodies. Arexvy® and Abrysvo® vaccines and nirsevimab (Beyfortus®) contain a small amount of polysorbate 80.

Mild illness without fever is not a contraindication. In the presence of an acute illness that has not yet been diagnosed, RSV vaccination can be postponed, as with all other vaccines.

Intramuscular injection may cause bleeding in people with thrombocytopenia and bleeding disorders.

**Question 7: What are some other important considerations for the administration of RSV vaccines and monoclonal antibodies?**

**• How can the currently approved RSV vaccines and monoclonal antibodies be administered simultaneously with other vaccines?**

Maternal RSV vaccines can be co-administered simultaneously with influenza vaccine, coronavirus disease-2019 (COVID-19) vaccine and/or anti-D immunoglobulin. There are some data to support that concomitant administration of RSV vaccine with pertussis-containing vaccine may result in a slightly reduced response to pertussis. When a pregnant woman who has previously received pertussis-containing vaccine presents for RSV vaccination, up to four weeks may be allowed between the two doses. When a pregnant woman who has not previously received pertussis-containing vaccine presents for RSV vaccination, the two vaccines should be given at the same time.

Monoclonal antibodies to RSV administered in neonatal and early infancy can be co-administered with routine vaccines administered in neonatal and early infancy.

RSV vaccines recommended for older age groups can be administered concurrently with pneumococcal vaccines and shingles (herpes zoster) vaccines. There is some evidence that concurrent administration of RSV vaccine with seasonal influenza vaccine may result in a reduced response to influenza. However, there is also evidence that COVID-19 vaccine reduces the response to RSV vaccine when administered concurrently. However, RSV vaccines can be administered concurrently with seasonal influenza and/or COVID-19 vaccines in older people when there is an urgent need for protection or when it is difficult for people to return to the health facility. Data on the immunogenicity and safety of concurrent administration with other vaccines is still limited. Immunization advisory committees of countries have different recommendations on this issue.

**• What is the duration of duration of protection of the currently approved RSV vaccines and monoclonal antibodies?**

Maternal antibodies produced by maternal vaccination provide protection for the newborn for approximately 5-6 months.

Clinical trials have shown that nirsevimab (Beyfortus®) has a duration of action of 5-6 months to prevent severe RSV-related illness (requiring medical care, hospitalization or intensive care admission). Palivizumab (Synagis®) has been shown to have a shorter duration of action than nirsevimab; therefore, a five monthly doses are required to provide protection during the RSV season.

Protein-based RSV vaccines recommended for older people appear to provide some protection for at least two RSV seasons so far. However, the duration of protection of the vaccine using the mRNA platform is still uncertain.

Additional systematic surveillance and measurement studies are needed to assess the duration of vaccine protection and the need for additional doses.

**• What are the defined risk groups for RSV disease for children aged 8-19 months who are recommended to receive nirsevimab (Beyfortus®) before the second RSV season?**

The United States Advisory Committee on Immunization Practices (ACIP) has identified these conditions as children with chronic lung disease due to prematurity who require medical care support up to six months before the start of the second RSV season, children with severe immunodeficiency, children with severe cystic fibrosis or below the 10$^{th}$ percentile, and American or Alaska Native children.

**• What are the specified high-risk conditions that increase the risk of severe lower respiratory tract disease due to RSV in people aged 60-74 years?**

According to ACIP, these conditions include chronic cardiovascular disease, chronic lung or respiratory disease, end-stage chronic kidney disease, diabetes mellitus with complications, neurological or neuromuscular conditions with impaired airway patency or respiratory muscle weakness, other conditions that increase the risk of severe lower respiratory tract disease due to RSV, such as chronic liver disease, chronic hematologic diseases, severe obesity, moderate or severe immunodeficiency, nursing home residents, and people with chronic disease conditions not diagnosed by health care providers or living in remote rural areas. Risk definitions and vaccine administration guidelines for risk groups under the age of 60 have not yet been published.

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