INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Prevention of Respiratory Syncytial Virus***
-August 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a review of agents approved for the prevention of Respiratory Syncytial Virus (RSV). The review focused on four approved agents; palivizumab, the long-acting monoclonal antibody nirsevimab, and the two RSV vaccines indicated for use in older adults. Currently, no medications for the prevention of RSV are listed on the IHS National Core Formulary (NCF); however all immunizations recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) are on formulary. Following evaluation and deliberation, the NPTC voted to **ADD "Long-acting monoclonal antibodies, All ACIP-recommended"** to the NCF**. Following the ACIP recommendation of nirsevimab, this agent is included on the NCF.**

Discussion:

Palivizumab, a monoclonal antibody indicated for RSV prevention, was FDA approved in 1998. The National Institute of Health's groundbreaking discovery of the structure of the RSV virus prefusion F protein in 2013 paved the way for the development of additional agents for the prevention of RSV.[6]

Epidemiology: RSV is a major cause of lower respiratory tract infections (LRTI), particularly in infants, children, elderly and those with chronic medical conditions. The data table below provides estimates of RSV impact in the US.[1]

Per year in USA	Deaths	Hospitalizations	Emergency room visits	Outpatient visits	Medical encounters
Children <5 years	100-300	58,000 – 80,000	520,000	1.5 million	
Adults ≥65 years	6,000 – 10,000	60,000-160,000			0.9 – 1.4 million

Numerous studies have shown an increased incidence (ranging from 4-10x higher) of RSV hospitalization in American Indian/Alaska Native (AI/AN) infants, particularly in Alaska and in Southwest US regions.[2] Adult AI/AN rates are not well studied. Real time RSV data can be found at the CDC's RSV-NET Interactive Dashboard.[3] Classic preventive measures for RSV illness include good hygiene, breastfeeding for passive immunity to the infant and palivizumab for select infants.[4, 5] Treatment guidelines encourage supportive care and hospitalization as needed for worsening respiratory status and/or fluid concerns.[4]

PEDIATRIC Approved Preventive Monoclonal Antibodies (mAB)

Palivizumab (Synagis®): approved in 1998 for select high risk infants. Administration is based on American Academy of Pediatrics guidelines for preterm infants <29 weeks gestational age or <32 weeks gestational age with chronic lung disease or hemodynamically significant cardiovascular disease.[7] It is administered monthly during the RSV season with up to 5 seasonal doses given.[7] A 2021 Cochrane review of palivizumab use reported a 56% reduction in hospitalizations and a 67% reduction of RSV infection rates at two-years' follow-up.[8] A systematic review of safety data in 2014 provided that the most common adverse events are injection site reactions and fever; no difference in adverse events compared to placebo were reported and palivizumab use was rarely discontinued due to adverse effects (0.3%).[9]

Nirsevimab (Beyfortus®): a new, long-acting RSV F protein-directed fusion inhibitor (monoclonal antibody) indicated for prevention of RSV disease in infants and children. It was approved by the FDA on July 17, 2023 and recommended by the ACIP on August 3, 2023.[10] Additional clinical considerations for use are expected to be published in the CDC's Morbidity and Mortality Weekly Report (MMWR) in the coming weeks.

The ACIP and AAP have provided the following joint guidance[19] for nirsevimab; (1) **use in all infants <8 months of age born during or entering their first RSV season**, and (2) use in children ages 8-19 months at increased risk of severe RSV disease and entering their second RSV season, including those recommended to receive palivizumab by AAP. The high risk groups include chronic lung disease of prematurity requiring medical support; severe immunocompromise; cystic fibrosis with severe lung disease; and AI/AN children.[11] **All AI/AN children are considered high risk and should receive a dose of nirsevimab as prevention for their 2nd RSV season.**[11] Per the FDA's labelling of nirsevimab, children who have received nirsevimab should not also receive palivizumab for the same RSV season. [11]

The first dose should be given in the first week of life for infants born shortly before and during RSV season; shortly before the start of RSV season for infants age <8 months of age; and shortly before the start of the second RSV season for children aged 8-19 months of age who are at increased risk of severe RSV disease, including all AI/AN infants/children. [11]

Data supporting nirsevimab use was reviewed and reported to the CDC[12] (derived from the Melody and Harmonie Studies). Nirsevimab decreased medically-attended RSV LRTI by 79% (95% CI: 68.5-86.1%); RSV LTRI with hospitalization by 80.6% (95% CI: 62.3-90.1%); and RSV LRTI with ICU admission by 90.0% (95% CI: 16.4-98.8%). No deaths were recorded due to RSV respiratory illness in the treatment arm.[12] Most commonly reported adverse reactions were injection site reaction (0.3%) and rash (0.9%). Reported safety events included pyrexia. No significant adverse events, no anaphylaxis or serious allergic reactions and no deaths were considered related to nirsevimab.[13] Contraindications and precautions can be found in the package insert.[14]

ADULT Approved Preventive Vaccines

In May 2023, the FDA approved two RSV vaccines for preventing LRTI for adults ≥ 60 years. Both vaccines utilize recombinant stabilized pre-fusion F protein as the RSV antigen; the RSV PreF3 vaccine (Arexvy®) also contains ASO1E adjuvant whereas RSV preF3 vaccine (Abrysvo®) is not adjuvanted.[15] On June 21, 2023, the CDC ACIP recommended that persons ≥60 years **may** receive one dose of either of the aforementioned new vaccines[15], using the ACIP's Shared Clinical Decision-Making Recommendations.[16] With shared decision-making, the determination to vaccinate an eligible individual should be based on a discussion between patient and provider, taking into consideration patient factors, provider clinical discretion, and the specific vaccine.[15]

A single dose of either RSV vaccine prevented symptomatic RSV LRTI with moderate to high efficacy in trials over two seasons; observed efficacy was less in the second season (see Table's 1 and 3). It is important to note that the composition and seasonal time frames were not the same, so close comparison is not possible. There were too few hospitalizations or deaths to determine efficacy for such.[15]

Overall, both vaccines were well tolerated in terms of reactogenicity and had acceptable safety profiles with regard to adverse events.[15] The most common adverse reactions observed in trials were similar between both vaccines;

- Arexvy® vaccine: injection site pain 60.9%, fatigue 33.6%, myalgia 28.9%, headache 27.2%, arthralgia 18.1%;
- Abrysvo® vaccine: fatigue 15.5%, headache 12.8%, injection site pain 10.5%, myalgia 10.1%.

The frequency of severe events was similar among vaccine and placebo recipients (see Table's 2 and 4).[15] A higher number of participants reported atrial fibrillation among vaccine recipients (n=10) than control participants (n=4) in trials of both vaccines. Inflammatory neurologic events were reported in three (of 17,922) Arexvy® recipients and three (of 20,255) Abrysvo® recipients during trials.[15] These events included Guillain-Barre syndrome, acute disseminated encephalomyelitis, Miller Fisher syndrome, and undifferentiated motor-sensory axonal polyneuropathy although the diagnosis was uncertain in several patients.[15] The vaccine trials were not large enough to determine whether there is an association between RSV vaccination and atrial fibrillation or neuroinflammatory events; post-marketing surveillance will occur to better assess risk.[15] More detail on these adverse events can be found in the MMWR's Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices.[15]

Given the current state of evidence, RSV vaccination in this population should be focused on those who are at greatest likelihood to benefit from vaccination given their increased risk of severe RSV disease due to underlying medical conditions or other factors as listed in the aforementioned MMWR document. The decision to vaccinate should be based on the patient-provider discussions regarding individual risk and patient preferences.[15] According to the CDC, given the unclear possible risk of inflammatory neurologic events observed in trials, RSV vaccination in this population should be focused on those who are at highest risk of severe RSV disease in order to maximize potential benefit.[15]

RSV vaccines are currently approved and recommended to be given as a single dose, ideally before the beginning of the RSV season. For the 2023-2024 season, RSV vaccination should be offered as soon as supply becomes available and should continue to be offered to eligible unvaccinated adults ≥60 years using shared clinical decision-making.[15] Co-administration of RSV vaccines with other adult vaccines is acceptable.[15]

The full report describing recommendations for use of RSV vaccines in older adults was published in the MMWR.[15] Other information is available in the manufacturer package inserts (Arexvy®, Abrysvo®).[17-18] Safety monitoring for these new RSV vaccines will utilize the Vaccine Safety Datalink and the Vaccine Adverse Event Reporting System (VAERS). Information about submitting adverse event reports can be found on the VAERS website.

Findings:

RSV vaccines and monoclonal antibodies are being developed to prevent RSV infection. Currently four are approved for use: palivizumab (mAB, approved 1998), nirsevimab (mAB, approved July 2023) - both for infants; and two RSV vaccines, Arexvy® and Abrysvo® (both approved in June 2023) for use in adults aged ≥60 years. The utilization of RSV preventive countermeasures should promote substantial and sustained reductions of RSV LTRI.

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