NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 11/13/2023
To: "Haben Debessai" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-2045

RE: Manuscript Number ONG-23-2045

What Obstetricians Need to Know About Respiratory Syncytial Virus

Dear Dr. Debessai:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below. The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting). Upload the tracked-changes version when you submit your revised manuscript.

Your submission will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by 11/27/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* As of January 2024, only certain article types will appear in the print version of the journal. All accepted articles will continue to publish online. All articles will be indexed in PubMed as an official article of Obstetrics & Gynecology. Additional information is available in the Instructions for Authors (https://journals.lww.com/greenjournal/Pages /InformationforAuthors.aspx#II).

REVIEWER COMMENTS:

Reviewer #1:

The authors present a narrative review focusing on recent developments in the prevention of RSV infection in infants. The manuscript is well written, and it offers valuable and current information for obstetricians. Below are my comments:

Lines 40 to 74: For enhanced clarity, I recommend explicitly detailing the intended patient populations for the RSV prevention options currently available.

Lines 47 to 85: I suggest providing a global perspective, comparing the US with other developed countries in terms of RSV prevalence, prevention, and management.

Lines 82 to 85: Why was the RSV pattern altered during COVID? Please provide a brief overview of possible causes.

Lines 90 to 103: What is an "F protein"? What other maternal vaccines produce transplacental transfer of antibodies? What was the actual incidence of medically attended severe RSV-associated LRTI in the vaccine and placebo group?

Lines 250 to 255: There's no information being compared in Boxes 1 and 2, I suggest formatting this as plain text as opposed to tables. Box 2 seems redundant; I would consider removing it.

Reviewer #2:

Abstract - no comments

Intro
--line 36 - I would specifically state the GA limits 32+0 to 36+6 to be abundantly clear in every place where GA is mentioned

--line 37 - beyfortus is misspelled

--line 41 - while I agree that the 2 RSV vaccines out there are confusing, the way this sentence is written does not clear it up. It would probably be easiest to say that there are 2 RSV vaccines, Abrysvo has pregnancy associated indication and an older adult indication, and Arexvy is for only RSV prevention in older adults.

Safety Efficacy
--line 89 - as above please spell out the gestational window in which vaccine can be administered

--is "dosing interval" the best description of the eligible gestational window ? It could be misinterpreted to mean multiple doses are given during that time frame. Perhaps this is the best term to use but pointing this out in case an alternative would be considered

--line 131 - can you include what is RSV season in most of the continental US ? October - March ?

--line 138 - the way Abrysvo is described here - bivalent, nonadjuvanted - is different than how it's been described in this paper to date - this actually makes me wonder if this is a different Abrysvo for older adults ? I can't imagine that to be the case and wonder what is the relevance of pointing here the valency of the vaccine and whether it's adjuvanted - if there is relevance to this, it would be helpful to discuss this earlier in the area when the vaccine is initially described (line 90)

--line 142 - this is confusing - since RSVpreF and RSV preF3 have similar appearances of the word, it might be easier just to keep referring to the vaccine of choice for preg as Abrysvo, as has previously been done in this paper to date

--re the safety signal for preterm birth - can the authors comment on any postulated mechanism ?

--can the authors also comment on what other vaccine platform this one most resembles, as this may help clinicians classify the type of vaccine better with such a comparison drawn?

--somewhere in the efficacy section can the authors comment on the minimum number of days elapsed between vaccination and delivery that counts as "vaccinated" for the baby ? It does not appear this was specifically reported in the NEJM trial but I'm not sure if it's been reported elsewhere.. or is "full vaccination" being extrapolated from our knowledge of other vaccines in pregnancy? (this comes up later in the article but would be worth addressing here)

--post marketing surveillance after RSV vax for HDP/PTB - is this something we as clinicians need to report somewhere? who is surveilling for the FDA ? can you provide more info on this / how this impacts the clinician ?

--storage info - can you discuss the implications of trying to carry it in your clinic ? are they single dose vials, does it need refrigeration, does it expire quickly etc ? I am sure many smaller practices haven't get received it and this info would be helpful to have.

Nirsevimab section
--what is the youngest age at which this can be given? birth hospitalization? does gestational age of the infant matter for administration ? is there a "usual time" of vaccination for normal low risk term baby? looks like indirectly based on the dose one has to be more than 5kg ? that will take some babies, even term babies, a long time to get to... perhaps this would play a role in our counseling. overall, some more logistic details about who gets it and when, beyond RSV seasonality, would be helpful

--is it possible to give more data on the patient population in the nirsevimab trial ? ie, to the same level of detail as is included in the RSV vaccine section, so we can equally compare generalizability to our patient population?

Discussion of options
--lines 192-194 - can you please provide some common scenarios in which transplacental transfer is known to be reduced, or what conditions don't result in an adequate immune response
- these are likely rare scenarios but this statement is vague and difficult to interpret and apply directly to the clinical setting, and may result in over-suspicion of "possibly inadequate fetal antibody levels" without this being based in fact

--line 199 - nirsevimab "upon delivery" - do we really mean to suggest that some high risk infants get it within 24h of life ? if that is the case that is fine, but I think some greater discussion regarding the nuance of nirsevimab administration considerations should be in the nirsevimab section.

Access
--line 214-215 - this statement regarding private insurers is not clear. They have to cover within 12 mo of the CDC's date, but does the ACA mandate it is retroactive to the date of the CDC approval? We are having ALOT of patients not have clarity on the coverage issue, and some are being charged $400+ out of pocket at area pharmacies, not $295. any more detail you can provide on legal requirements for coverage of this vaccine would be helpful to clinicians counseling their patients where there is a lot of uncertainty, even after the pt calls the insurance company

General comments
--I'm curious on the authors perspective of the COVID pandemic on the vaccine efficacy numbers. The RSV vax trial was during some peak COVID times when many pts were isolating themselves postpartum to avoid COVID, consequently avoiding RSV - wondering if the nirsevimab trial was ongoing during the COVID pandemic also, when exposure risks were different - wondering if the authors will comment

box 1
--advantage of Abrysvo - "more resistant to virus mutations" could be misunderstood as being a double negative somehow - maybe just spin the positive, may have broader coverage against different RSV strains ?

--disadvantage of Abrysvo - is maternal HIV that is well controlled, undetectable VL, really an immunocompromised state with less maternal antibody response to vaccination ? is this also true about autoimmune conditions as an umbrella term ? I am concerned that these statements, in the absence of data, will lead patients, providers to think that whole categories of patients can't have an adequate vaccine response in pregnancy which I don't think is true - can we be more specific, especially in the text, about which subpopulations we might truly be concerned don't respond to any immunization in pregnancy ?

--can you clarify why we think nirsevimab effect would last longer than Abrysvo ? primary outcome is 150d after nirsevimab (efficacy 79%) vs 180d after birth for those with 32-36w RSV vax in preg (efficacy 77%) - admittedly prespecified subgroup - but the time zeros are relatively similar between the 2 groups, with relatively similar efficacies - maybe there is other data but from this data it doesn't seem clear to me that we know what's better, but this chart makes it seem like nirsevimab is better - possibly longer protection, no risks of preterm birth etc... I think there is a lot of uncertainty which is ok to acknowledge, and what might also factor in the decision making is patient specific factors, which isn't mentioned in this counseling table. ie, if you're going to have a 35w delivery for accreta, should you get it in pregnancy, or how soon can your baby get it after birth ? as above, the latter info is not discussed

box 3
-- I am not sure that this helps the clinician as it doesn't get into the nuance on risk/benefit, possible safety signal for HDP/PTB, vaccine/monoclonal ab efficacy, safety demonstrated of vaccination in preg - which are all the common questions pts ask about this vaccine.

--
Sincerely,

Torri D. Metz, MD, MS
Deputy Editor, Obstetrics

The Editors of Obstetrics & Gynecology

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

November 16, 2023

Dear Dr. Jason Wright:

Please find enclosed the above Narrative Review entitled “What Obstetricians Need to Know About Respiratory Syncytial Virus” for consideration in its revised form. The manuscript, as submitted, is not under consideration for publication elsewhere and will not be submitted elsewhere while under consideration by *Obstetrics & Gynecology,* unless the journal allows for a preprint version. All authors have made substantive contributions to the manuscript and all authors endorse the information included. All disclosures have been stated. Revisions and corresponding responses are below and correlate with the tracked version of the article.

Thank you for considering this manuscript.

Sincerely,
Haben Debessai, MD

—

REVIEWER COMMENTS:
Thank you very much for your consideration and review of this article, our responses to all reviewer comments and revisions are included below.

Reviewer #1:

The authors present a narrative review focusing on recent developments in the prevention of RSV infection in infants. The manuscript is well written, and it offers valuable and current information for obstetricians. Below are my comments:

Reviewer 1 Point 1:
Lines 40-74: For enhanced clarity, I recommend explicitly detailing the intended patient populations for the RSV prevention options currently available.

Thank you for this suggestion.

Line 44: The addition of “in infants” has been added for specificity in the target population for these options.

Line 83: Addition of “in this article” to specify target population of discussion in this paper in addition to mention of RSV infection in other populations. These edits have been made to clarify that the focus of this article is to discuss the prevention options of RSV LRTI in infants in young children. We do include information on the other available RSV vaccine, Abrysvo as well since both are recommended for non-pregnant adults (≥60 years old).

Reviewer 1 Point 2:

Lines 47-85: I suggest providing a global perspective, comparing the US with other developed countries in terms of RSV prevalence, prevention, and management.

Thank you for this suggestion. Respectfully, we would prefer to focus on US data rather than global scope in this article given the current recommendations are for US providers as the intended audience. We added this to clarify this pertains to U.S providers.

Reviewer 1 Point 3:

Lines 82-85: Why was the RSV pattern altered during COVID? Please provide a brief overview of possible causes.

Thank you for this comment.

Lines 99-103: The RSV pattern was altered during COVID due to increased isolation, masking, increased hand hygiene and other non-pharmaceutical personal protective measures that affected RSV transmission. The following addition has been made to the manuscript to address this. “This pattern was altered during the COVID-19 pandemic because of nonpharmaceutical interventions (e.g. masking, reduced social gathering), with low levels of circulation during 2020-2021 and an earlier and longer season during 2021-2022; however, data from the 2022-2023 season and early data from the 2023-2024 season suggest that seasonal patterns are returning to those seen in pre-pandemic years.” References to https://emergency.cdc.gov/han/2023/han00498.asp and Hamid et. al., article http://dx.doi.org/10.15585/mmwr.mm7214a1

Reviewer 1 Point 4:

Lines 90-103: What is an "F protein"? What other maternal vaccines produce transplacental transfer of antibodies? What was the actual incidence of medically attended severe RSV-associated LRTI in the vaccine and placebo group?

Thank you for this comment.

Lines 108-109: An F protein is a type of fusion protein that allows for viral penetration of the respiratory epithelial host cell and the vaccine contains a recombinant stabilized prefusion version of this which results in a strong neutralizing response in the vaccine recipients. This explanation has been added to the manuscript.

Line 93-94: Addition of “previous studies have shown that effective transplacental transfer of maternal antibodies occurs with administration of other maternal vaccines in the second and third trimester (e.g., anti SARS-CoV-2 antibodies after Covid-19 vaccination)” is given for an example https://www.sciencedirect.com/science/article/pii/S0264410X23006989?via%3Dihub

Lines 119-121: Incidences have been added for medically attended severe RSV-associated LRTI in the vaccine vs. placebo group: “vaccine efficacy for medically attended severe RSV-associated LRTI in the infant was reported at 81.1% (99.5% CI, 40.6 to 96.3) from 0–90 days of life with 6 affected infants in the vaccine group vs. 33 in the placebo group and 69.4% (99.5% CI, 44.3 to 84.1) from 0–180 days of life

with 19 affected infants in the vaccine group vs. 62 in the placebo group" (Kampmann et. al.).

Reviewer 1 Point 5:

Lines 250-255: There's no information being compared in Boxes 1 and 2, I suggest formatting this as plain text as opposed to tables. Box 2 seems redundant; I would consider removing it.

Thank you for this revision.
Line 301: We would prefer to keep *Box 1* as it provides useful information on the comparison of the relatives advantages and disadvantages of each prevention option in a succinct format for providers to utilize easily. We added the word "relative" to describe the advantages and disadvanatages in box 1. At your suggestion, we have removed *Box 2* and added the links (VAERS safety monitoring website & V-safe, MotherToBaby, and CDC commonly FAQs) into the article as they are mentioned (lines: 142, 242, and 296, respectively)

Reviewer #2:

Reviewer 2 Point 1:

Abstract - no comments

Reviewer 2 Point 2:

Intro

Line 36- I would specifically state the GA limits 32+0 to 36+6 to be abundantly clear in every place where GA is mentioned

Line 36: Thank you for pointing this out. This has been altered throughout the paper to 32-0/7 to 36-6/7 for gestational age

Reviewer 2 Point 3:

Line 37 - beyfortus is misspelled

Line 37: This has been corrected, thank you.

Reviewer 2 Point 4:

Line 41 - while I agree that the 2 RSV vaccines out there are confusing, the way this sentence is written does not clear it up. It would probably be easiest to say that there are 2 RSV vaccines, Abrysvo has pregnancy associated indication and an older adult indication, and Arexvy is for only RSV prevention in older adults.

Line 169-171: Thank you for the revision. Clarification has been made with the following statement further in the paper to limit confusion an provide clarity on which RSV vaccine is recommended in pregnancy: "While only one vaccine, Abrysvo, is approved for use during pregnancy, two vaccines, Abrysvo (Pfizer) and Arexvy (GSK), are available for prevention of RSV LRTI in adults aged 60 years and

older, a group at substantial risk of RSV-associated morbidity and mortality."

Reviewer 2 Point 5:

Safety Efficacy

Line 89 - as above please spell out the gestational window in which vaccine can be administered

Line 107: The gestational age window of 32-0/7 to 36-6/7 weeks' has been added.

Reviewer 2 Point 6:

Is "dosing interval" the best description of the eligible gestational window ? It could be misinterpreted to mean multiple doses are given during that time frame. Perhaps this is the best term to use but pointing this out in case an alternative would be considered

Thank you for this suggestion.

Line 128 and 146-149: The wording has been clarified for the intended audience. The language was changed to "trial" and "approved" gestational age window. Previous wording was taken from language used in the ACIP presentation and MMWR (Use of the Pfizer Respiratory Syncytial Virus Vaccine During Pregnancy for the Prevention of Respiratory Syncytial Virus–Associated Lower Respiratory Tract Disease in Infants: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)).
The wording has been altered to be more clear for the intended audience. Has been changed to "trial gestational age window;" and "approved gestational age window".

Reviewer 2 Point 7:

Line 131 - can you include what is RSV season in most of the continental US ? October - March ?

Thank you for this question.

Line 158: The RSV season differs each year because it is defined by disease prevalence (~3% indicates the beginning) and this differs across regions of the United States. For ease in determining the timing appropriate for RSV vaccination, CDC determined the timeline based on general trends in the United States. The tail end of the RSV season is also highly variable because it depends on decreased disease prevalence. During the tail end of the season when transmission is decreasing, immunization is relatively less important than during the early or peak times of RSV transmission which is how the RSV timing of administration was determined. Due to this complexity (which may not be relevant for the practicing OBGYN), CDC generally uses the wording that the RSV season is "typically during the Fall through Spring" which has been added to the manuscript. We chose this to minimize any confusion about the timing for administration of RSV vaccine.

Reviewer 2 Point 8:

Line 138 - the way Abrysvo is described here - bivalent, nonadjuvanted - is different than how it's been described in this paper to date - this actually makes me wonder if this is a different Abrysvo for

older adults ? I can't imagine that to be the case and wonder what is the relevance of pointing here the valency of the vaccine and whether it's adjuvanted - if there is relevance to this, it would be helpful to discuss this earlier in the area when the vaccine is initially described (line 90)

Line 171-172: Thank you for this revision. The valency and adjuvant specification for each option has been removed due to lack of relevancy for the focus of the article. The Abrysvo vaccine is the same regardless of whether it is administered to a 60+ year old adult or a pregnant person.

Reviewer 2 Point 9:

Line 142 - this is confusing - since RSVpreF and RSV preF3 have similar appearances of the word, it might be easier just to keep referring to the vaccine of choice for preg as Abrysvo, as has previously been done in this paper to date

Thank you for pointing this out.

Line 105: The change from using RSVPreF vaccine to Abrysvo has been made throughout the paper. This article will use the brand name for both the maternal vaccine (Abrysvo) and the nirsevimab (Beyfortus) to provide consistency and to minimize confusion between vaccines.

Reviewer 2 Point 10:

Re the safety signal for preterm birth - can the authors comment on any postulated mechanism?

Thank you for this question.

Respectfully, we would prefer not to include a proposed mechanism in this manuscript because it is unknown if this is a real finding. Postulating a mechanism could imply that we believe this is a clinically significant finding which we feel would be inappropriate without additional data.

Reviewer 2 Point 11:

Can the authors also comment on what other vaccine platform this one most resembles, as this may help clinicians classify the type of vaccine better with such a comparison drawn?

Thank you for this question.

Line 89-90: Numerous vaccines use recombinant proteins, including certain flu and Hep B vaccines. This has been added: "Other recombinant protein vaccines include certain influenza and hepatitis B vaccines." If you are asking about other vaccines that use a similar mechanism to produce the recombinant proteins, both Abrysvo and Shingrix vaccines use Chine Hamster Ovary cells to grow the recombinant protein antigen. We are unaware of any differences in efficacy or safety associated with differing protein production technologies (e.g., E. coli, yeasts, insect cells).

Reviewer 2 Point 12:

Somewhere in the efficacy section can the authors comment on the minimum number of days elapsed

between vaccination and delivery that counts as "vaccinated" for the baby ? It does not appear this was specifically reported in the NEJM trial but I'm not sure if it's been reported elsewhere.. or is "full vaccination" being extrapolated from our knowledge of other vaccines in pregnancy? (this comes up later in the article but would be worth addressing here)

Thank you for this comment.

Line 113-115: Changes were made to clarify and highlight the 14-day minimum that is recommended for antibody transfer to the fetus "It is believed that at least 14 days are needed between maternal vaccination and delivery to confer infant protection." The Kampann NEJM article (Kampmann B, Madhi SA, Munjal I, Simoes EAF, Pahud BA, Llapur C, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med 2023 Apr 20;388(16):1451-64) specifies that "The evaluable population consisted of all infant participants who were eligible, were born to the maternal participants who had received the randomly assigned vaccine or placebo at least 14 days before delivery…" The authors are unaware of data specific to RSV vaccines, but this criteria was likely based on data for other vaccines (e.g, Tdap: https://academic.oup.com/cid/article/53/9/885/346318). CDC's website on vaccines during and after pregnancy states: "it takes about 2 weeks after getting vaccinated before the body develops antibodies" (Routine and Influenza Immunization Services During the COVID-19 Pandemic: Interim Guidance | CDC).

Reviewer 2 Point 13:

Post marketing surveillance after RSV vax for HDP/PTB - is this something we as clinicians need to report somewhere? who is surveilling for the FDA ? can you provide more info on this / how this impacts the clinician ?

We have added information.

Line 141-144: "FDA is requiring monitoring and post-marketing studies to assess the signals of preterm birth and hypertensive disorders of pregnancy which can be reported to the Vaccine Adverse Event Reporting System (VAERS).[1] Additionally, V-safe is a CDC program that allows individuals to share their experiences following vaccination; providers can direct vaccinated persons to the site or share printed materials."

There are several ways postmarketing surveillance is being conducted. These were presented to ACIP and are publicly available: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-22/02-Mat-Peds-DeSilva-508.pdf and https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-22/03-Mat-Peds-Moro-508.pdf. Additionally, FDA has stated that "The FDA is requiring the company to conduct postmarketing studies to assess the signal of serious risk of preterm birth and to assess hypertensive disorders of pregnancy, including pre-eclampsia." https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants

Reviewer 2 Point 14:

Storage info - can you discuss the implications of trying to carry it in your clinic ? are they single dose vials, does it need refrigeration, does it expire quickly etc ? I am sure many smaller practices haven't get received it and this info would be helpful to have.

Thank you for this comment.

Line 165-168: The addition of storage information has been made" Abrysvo is supplied in a kit with a prefilled syringe and sterile water diluent component for reconstitution, which should be stored at 2°C to 8°C until reconstituted, at which point it can be kept at room temperature; it should be used within 4 hours.[34] The shelf life is 24 months from the time of production." These recommendations are according to the FDA approval letter for Abrysvo. Of note, the shelf life of the vaccine as 24 months from the time of production will vary depending on when it is purchased. We have also reached out to Pfizer to see if there is a more specific manufacturer recommendation.

Reviewer 2 Point 15:

Nirsevimab section

What is the youngest age at which this can be given? birth hospitalization? does gestational age of the infant matter for administration ? is there a "usual time" of vaccination for normal low risk term baby? looks like indirectly based on the dose one has to be more than 5kg ? that will take some babies, even term babies, a long time to get to... perhaps this would play a role in our counseling. overall, some more logistic details about who gets it and when, beyond RSV seasonality, would be helpful

Thank you for this comment.

Line 190-192: Additions to the recommendations include: Beyfortus to be administered "within first week of birth" which applies to those born during the RSV season (Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)). And for infants aged <8 months born outside the RSV season, Beyfortus administration is recommended shortly before the RSV season. Previous language was referring to the 100mg dose, since those are the recommendations that were changed due to shortages specific to the 100mg dose. There are no special limitations on receiving the vaccine for those born premature or gestational age < 37 weeks.

Line 207: Information on weight and dosing recommendations have also been included: "Recommendations for the 50mg dose of Beyfortus (for infants <5kg) remain unchanged."

Reviewer 2 Point 16:

Is it possible to give more data on the patient population in the nirsevimab trial ? ie, to the same level of detail as is included in the RSV vaccine section, so we can equally compare generalizability to our patient population?

Thank you for this comment.

Both studies were multi-country studies that investigated medically attended LRTI and hospitalizations. The RSV vaccine section of the paper has both group (24-36 weeks') and subgroup (32-36 weeks') analysis of medically attended LRTI and hospitalization data at 0-90 and 0-180 days and data for hypertensive disorders of pregnancy and preterm birth. . The nirsevimab section of this paper also described the efficacy against medically attended LRTI and hospitalization, but the published studies only report efficacy at 150 days after injection (i.e., there is no reporting of efficacy for any other

timeframes).

Reviewer 2 Point 17:

Discussion of options

Lines 192-194 - can you please provide some common scenarios in which transplacental transfer is known to be reduced, or what conditions don't result in an adequate immune response

- these are likely rare scenarios but this statement is vague and difficult to interpret and apply directly to the clinical setting, and may result in over-suspicion of "possibly inadequate fetal antibody levels" without this being based in fact

Thank you for this revision.

The authors agree that defining reduction in transplacental transfer is challenging in the absence of data and may be variable. Given the lack of data to define the specific groups of pregnant women or conditions in which this can occur with RSV vaccine, the authors have indicated that an individualized decision would need to be made in this situations, to define if both the RSV vaccine and the monoclonal antibody should both be given. Given that each clinical situation may be unique and more data are needed to define the population, it is not possible to define these subgroups now. However, CDC does recommend that nirsevimab be considered in infants whose mothers were vaccinated if there are concerns about passive antibody transfer, depending on the clinical situation.

Line 232-236: The following addition has been made: "if maternal vaccination occurs in a pregnant person who lacks the ability to mount an adequate immune response or who has a condition associated with reduced transplacental antibody transfer (e.g., hypergammaglobulinemia), consultation with maternal-fetal medicine may be appropriate, and pediatricians may recommend Beyfortus for the infant."

Reviewer 2 Point 18:

Line 199 - nirsevimab "upon delivery" - do we really mean to suggest that some high risk infants get it within 24h of life ? if that is the case that is fine, but I think some greater discussion regarding the nuance of nirsevimab administration considerations should be in the nirsevimab section.

Thank you for this comment.

Line 190: Nirsevimab can be given in the first 24 hours of life, but the recommendation does mean that it must be given during this timeframe, only that it should be given **after birth** or "within one week of birth" either inpatient before discharge or in the outpatient setting (Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)).

Reviewer 2 Point 19:

Access

Line 214-215 - this statement regarding private insurers is not clear. They have to cover within 12 mo of the CDC's date, but does the ACA mandate it is retroactive to the date of the CDC approval? We are having ALOT of patients not have clarity on the coverage issue, and some are being charged $400+ out

of pocket at area pharmacies, not $295. any more detail you can provide on legal requirements for coverage of this vaccine would be helpful to clinicians counseling their patients where there is a lot of uncertainty, even after the pt calls the insurance company

Thank you for this comment.

Line 256-258: Based on the information we have, payers have approximately 12 months after CDC recommends a product to cover it. As far as we know, this does not mean that payers have to retroactively reimburse for the product but rather begin to cover it within this timeframe. The timeframe for insurers to cover the vaccine may vary which is why it is important that patients check with their specific insurer. According to Pfizer, 90% of insured persons have coverage for Abrysvo. We have added, "In addition, in accordance with the Affordable Care Act (ACA), private insurers are required to cover Abrysvo beginning 12 months after the date of CDC's recommendation."

Reviewer 2 Point 20:

General comments

--I'm curious on the authors perspective of the COVID pandemic on the vaccine efficacy numbers. The RSV vax trial was during some peak COVID times when many pts were isolating themselves postpartum to avoid COVID, consequently avoiding RSV - wondering if the nirsevimab trial was ongoing during the COVID pandemic also, when exposure risks were different - wondering if the authors will comment

Thank you for this comment.

In regards to the RSV vaccine trial (Kampmann article: Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants - PubMed (nih.gov), the trial period was June 2020-Oct 2022. It is stated that medically attended RSV-associated LRTI within 180 days after birth constituted only 22% of medically attended LRTI due to any cause in the same time period. In comparison, a prepandemic study of LRTI, RSV was the most common pathogen and in 50-80% of hospitalizations for bronchiolitis and 40% of cases of pneumonia among children <1 year old. RSV was less likely to be a cause of all-cause LRTI during the trial compared with pre-pandemic times. However, vaccine efficacy should not be affected given that both the vaccine and placebo groups are affected by pandemic (PPE use, isolation, etc.)

In regards to the nirsevmab studies: The paper from Griffin et. al., the preterm group (24-34 weeks' gestation) was prepandemic (November 2016- November 2017) and the later preterm/term study group was also prepandemic (July 2019 – November 2019) as referenced in the Hammit et. al., paper and the follow up group data from the MELODY trial was stopped during the pandemic (Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants | NEJM)

Line 99-101: The article includes reference to the effect COVID-19 pandemic and has had on RSV prevalence with the addition shown here: "This pattern was altered during the COVID-19 pandemic because of nonpharmaceutical interventions (e.g. masking, reduced social gathering)." It also contains references that include dates of the trial for further knowledge.

Reviewer 2 Point 21:

box 1

Advantage of Abrysvo - "more resistant to virus mutations" could be misunderstood as being a double negative somehow - maybe just spin the positive, may have broader coverage against different RSV strains ?

Thank you for this comment.

Line 301: Given that nirsevimab has only been studied and found to be resistant among current RSV strains, will change to “more resistant to potential virus mutations” and that both prevention options are highly protective.

Reviewer 2 Point 22:

Disadvantage of Abrysvo - is maternal HIV that is well controlled, undetectable VL, really an immunocompromised state with less maternal antibody response to vaccination ? is this also true about autoimmune conditions as an umbrella term ? I am concerned that these statements, in the absence of data, will lead patients, providers to think that whole categories of patients can't have an adequate vaccine response in pregnancy which I don't think is true - can we be more specific, especially in the text, about which subpopulations we might truly be concerned don't respond to any immunization in pregnancy ?

Thank you for this comment.

Line 232-236: Maternal HIV is indeed a complex topic in which to discuss transplacental transmission of antibodies. Decreased response can be seen in both treated and untreated (or inadequately treated populations but this may vary by disease severity, viral load and CD4 count. (Atwell JE, Lutz CS, Sparrow EG, Feikin DR. Biological factors that may impair transplacental transfer of RSV antibodies: Implications for maternal immunization policy and research priorities for low- and middle-income countries. Vaccine 2022 Jul 30;40(32):4361-70). Given the lack of current data to address each individual autoimmune condition, the authors include the recommendations as cited in the CDC MMWR. Also addressed above in Reviewer 2 Point 17 response

Reviewer 2 Point 23:

Can you clarify why we think nirsevimab effect would last longer than Abrysvo ? primary outcome is 150d after nirsevimab (efficacy 79%) vs 180d after birth for those with 32-36w RSV vax in preg (efficacy 77%) - admittedly prespecified subgroup - but the time zeros are relatively similar between the 2 groups, with relatively similar efficacies - maybe there is other data but from this data it doesn't seem clear to me that we know what's better, but this chart makes it seem like nirsevimab is better - possibly longer protection, no risks of preterm birth etc... I think there is a lot of uncertainty which is ok to acknowledge, and what might also factor in the decision making is patient specific factors, which isn't mentioned in this counseling table. ie, if you're going to have a 35w delivery for accreta, should you get it in pregnancy, or how soon can your baby get it after birth ? as above, the latter info is not discussed

Thank you for this important comment.

Waning of maternal vaccine-induced immunity in the infant from maternal vaccination has been described in pregnant patients who have received the influenza or Covid-19 vaccination (Nunes MC, Madhi SA. Prevention of influenza-related illness in young infants by maternal vaccination during pregnancy. F1000 Res 2018;7:122; Zerbo O, Ray GT, Fireman B, et al. Maternal SARS-CoV-2 vaccination and infant protection against SARS-CoV-2 during the first six months of life. Nat Commun 2023;14:894.). The maternal RSV vaccine trial (Kampmann et al) shows waning in efficacy from the 0-180 day to the 0-90 day trials (e.g., vaccine efficacy 81.8%, 99.5% CI: 40.6 to 96.3 in 0-90 days for medically attended severe RSV-associated LRTI to 69.4%, 97.58% CI: 44.3 to 84.1 in 0-180 days). Per available data, there is no evidence of waning protection during the first 150 days in the nirsevimab trials. Additionally, due to engineering of the Fc portion nirsevimab, the half life of nirsevimab has been extended beyond that of naturally occurring antibodies (to 68.7 days for nirsevimab compared with ~36-38 days for maternal-induced antibodies (https://www.nejm.org/doi/full/10.1056/nejmoa1913556). As a result, the nirsevimab trial demonstrated that the nirsevimab recipients had >7-fold high RSV neutralizing antibody levels 361 days after injection compared with baseline (https://www.nature.com/articles/s41591-023-02316-5).

Line 301: Box 1: However, given that we don't have any head to head trials comparing the two options and no data to show waning of nirsevimab in comparison to the vaccine directly, we cannot state one has improved efficacy over the other and would take care not to dissuade providers towards one option more than the other. This is why we would recommend maintaining wording to include "may last longer that maternal vaccination" as a relative advantage of Beyfortus

Box 3: Thank you. This box has been removed due to lack of ability to include detailed discussion on the nuances of decisions, will instead direct providers to FAQ links which cover these topics.

Line 295-296: Link to RSV (Respiratory Syncytial Virus) Immunizations | CDC website has been included to offer providers further information on how to counsel patients such as frequently asked questions (FAQs).

Reviewer 2 Point 24:

box 3

I am not sure that this helps the clinician as it doesn't get into the nuance on risk/benefit, possible safety signal for HDP/PTB, vaccine/monoclonal ab efficacy, safety demonstrated of vaccination in preg - which are all the common questions pts ask about this vaccine.

Thank you for this clarity, given that this nuanced conversation was missing valuable details that would be important to include, the authors have opted to remove the box (*Box 3)* in its entirety.