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May 11, 2023

VIA EMAIL AND FDA DOCKET FDA-2023-N-1338

Members, Vaccines and Related Biological
Products Advisory Committee
Food and Drug Administration
VRBPAC@fda.hhs.gov
CBERVRBPAC@fda.hhs.gov

Re: *May 18, 2023 VRBPAC Committee Meeting – Recommendations on the Safety and Effectiveness of Abrysvo in Pregnant Women and Infants*

Dear VRBPAC Members:

We write on behalf of our client, Informed Consent Action Network (**"ICAN"**), to bring to your attention several serious concerns about the safety and effectiveness of Pfizer's Respiratory Syncytial Virus Vaccine, Abrysvo, in advance of your meeting on May 18, 2023, during which you will discuss and make recommendations concerning Abrysvo for use in infants from birth through 6 months of age by immunization of pregnant women.

Pfizer's published study concludes that, "RSVpreF vaccine [Abrysvo] administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified." However, ICAN raises the following efficacy and safety concerns with this committee.

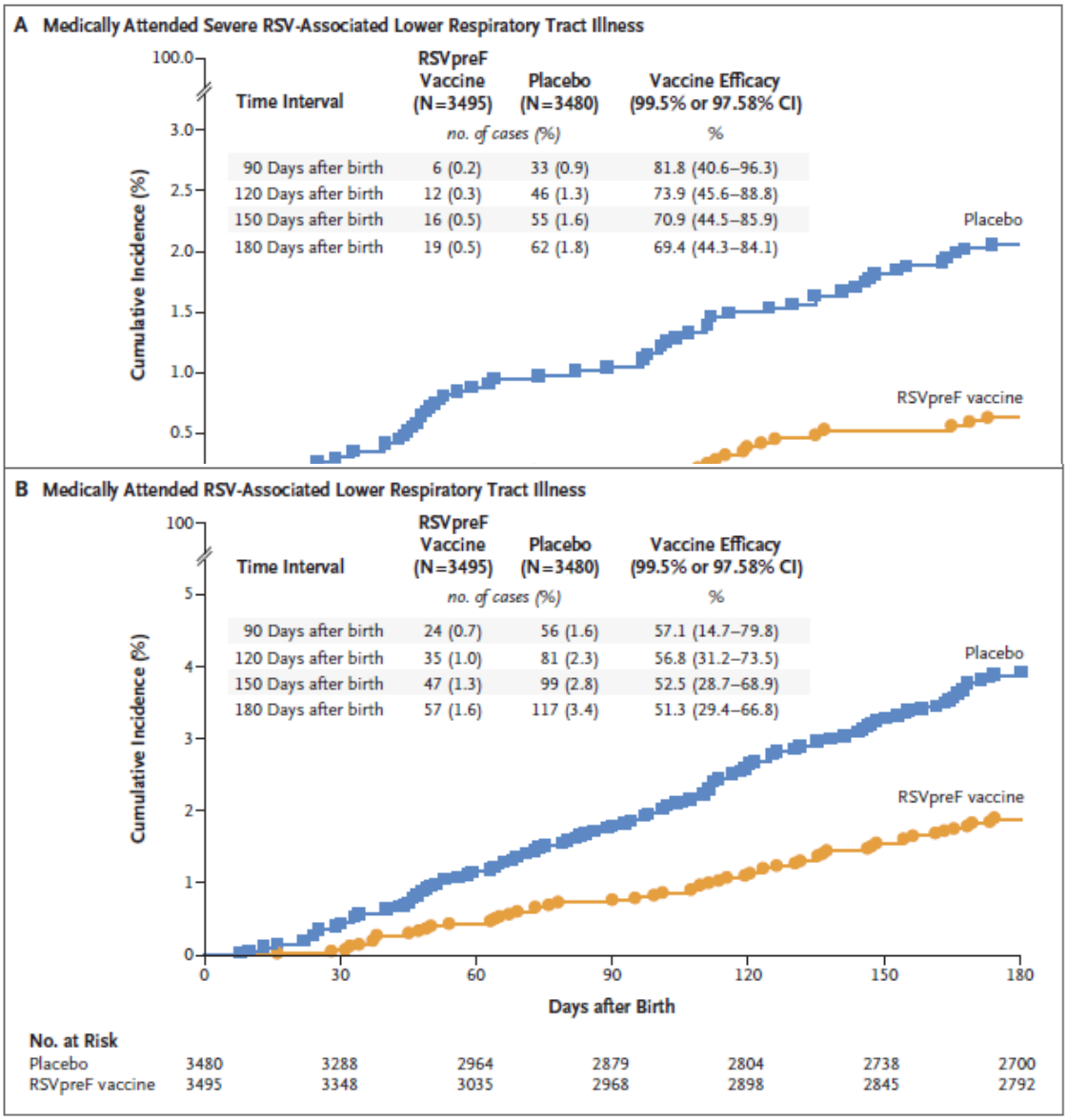
I. EFFICACY

First, it is crucial to note that the claimed 57.1% efficacy against "[m]edically attended RSV-associated lower respiratory tract illness … within 90 days after birth … **did not meet the statistical success criterion**."[1] Therefore, because "the criterion for vaccine efficacy was not met" for this crucial second primary end point (with the lower end of the confidence interval being an incredible 14.7%), **under no circumstances** should VRBPAC be relying on the results of this study to make recommendations about this vaccine for some of the most vulnerable individuals in America – infants aged three months and younger.[2]

[1] Beate Kampmann, M.D., Ph.D., et. al., *Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants*, New England J. Med. 1 (Apr. 5, 2023), https://www.nejm.org/doi/pdf/10.1056/NEJMoa2216480 (emphasis added).

[2] *Id.* at 12.

Equally concerning is that this study makes clears that the vaccine, like other respiratory disease vaccines, cannot generate sterilizing immunity and that any purported efficacy against medically attended severe lower respiratory illness appears to markedly wane even during the short duration of the study.[3]



[3] *See id.* at 8 (Tables); *see also* David M. Morens, et. al., *Rethinking next-generation vaccines for coronaviruses, influenzaviruses, and other respiratory viruses*, Cell Host & Microbe (Jan. 11, 2023), Vol. 31, Issue 1, 146-47 ("After more than 60 years of experience with influenza vaccines, very little improvement in vaccine prevention of infection has been noted. . . our best approved influenza vaccines would be inadequate for licensure for most other vaccine-preventable diseases. . . . However, as variant SARS-CoV-2 strains have emerged, deficiencies in these vaccines reminiscent of influenza vaccines have become apparent…. Considering that vaccine development and licensure is a long and complex process requiring years of preclinical and clinical safety and efficacy data, the limitations of influenza and SARS-CoV-2 vaccines remind us that **candidate vaccines for most other respiratory viruses have to date been insufficiently protective for consideration of licensure, including candidate vaccines against RSV**, a major killer of infants and the elderly." (emphasis added)).

Original antigenic sin is therefore a concern. These facts should be front and center of VRBPAC's discussion on this vaccine.

Crucially, as was the case with the Covid-19 vaccines, the study's claimed efficacy uses relative risk reduction in lieu of absolute risk reduction. This is both highly inappropriate and severely misleading in determining a risk/reward calculation for a vaccine. Absolute risk reduction is critical to gauge whether a vaccine should be administered to healthy individuals.

In this case, just 0.9% of infants in the placebo group had severe RSV 90 days after birth, whereas 0.2% did in the vaccinated group. Thus, the **absolute** risk reduction of severe RSV is just 0.7%. This means that the vaccine would purportedly allow just 7 infants per 1,000 to avoid severe RSV. Likewise, just 1.6% of infants in the placebo group had non-severe, medically attended RSV 90 days after birth, whereas 0.7% did in the vaccinated group. Thus, the absolute risk reduction of non-severe, medically attended RSV was just 0.9%, meaning that just 9 infants per 1,000 would avoid going to the doctor.

Ultimately, however, what is deeply significant is the study's finding that medically attended lower respiratory tract infection from any cause was essentially identical between the vaccine and placebo groups. As the study itself states: "RSVpreF vaccination **did not prevent** medically attended lower respiratory tract illness from any cause within 90 days after birth (vaccine efficacy, 7.0%; 99.17% CI, −22.3 to 29.3) (Table S8)."[4] If Abrysvo worked as well as is claimed in this study, one would expect an overall risk reduction for lower respiratory tract infections. This point must be considered prior to any recommendation for this population.

II. SAFETY

Although the study claims that "[n]o safety signals were detected," the study data itself belies those claims.[5] In infants, there was a 2.6% increase in any adverse event in the vaccinated group over the placebo, a 0.7% increase in severe adverse events, and a 0.3% increase in serious adverse events. In mothers, there was a 0.7% increase in the vaccinated group over the placebo, a 0.4% increase in severe adverse events, and 0.5% increase in serious adverse events.

Crucially, because the benefits of the vaccine were measured, via efficacy, for a period of three months and adverse events were measured for only one month, this had the effect of slanting the risk/benefit ratio in the vaccine's favor. But nevertheless, the safety signal is glaring with this vaccine.

The adverse events suffered by the study participants were indeed severe. In infants, adverse events included newborn transient tachypnea, respiratory distress, low birth weight, hypoglycemia, prematurity, and sepsis, the most common of which was jaundice. Yet, the study

[4] *Id.* at 8 (emphasis added).

[5] *Id.* at 1.

states that "[n]o serious adverse events in infants were considered by the investigator to be related to the vaccine."[6]

In mothers, serious adverse events included prolonged labor, premature delivery, postpartum hemorrhage, arrested labor, and gestational hypertension, the most frequent of which were preeclampsia and fetal distress. Preeclampsia is, of course, a gravely serious and life-threatening disorder that results in 16% of maternal deaths in high-income countries and 9%-26% of maternal deaths in low-income countries, as well as over 500,000 fetal deaths worldwide.[7] Alarmingly, ten mothers in the study experienced stillbirths (versus eight in the placebo group) and one vaccinated mother died from postpartum hemorrhage and hypovolemic shock.

Yet, again, the study investigator only found the following were related to the vaccine:

> Serious adverse events in four RSVpreF vaccine recipients (pain in an arm followed by bilateral lower-extremity pain, premature labor, systemic lupus erythematosus, and eclampsia — in one recipient each) and in one placebo recipient (premature placental separation) were assessed by the investigator as being related to the injection.
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> …
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> The only adverse events that were considered by the investigator to be related to the RSVpreF vaccine and that were reported in more than one maternal recipient in either group were lymphadenopathy and injection-site bruising (each reported in two RSVpreF recipients [<0.1%]). One adverse event (<0.1%) (prematurity) in an infant was considered by the investigator to be related to maternal RSVpreF vaccination.[8]

In terms of absolute risk/reward, for every seven cases of severe RSV the vaccine prevented (out of 1,000 vaccinated), it causes seven severe adverse events in infants; four severe adverse events and two life-threatening results in mothers; approximately nine premature births; and approximately six low birth weights. Put plainly, the risk/benefit assessment is negative. In light of this, it is deeply troubling that the authors state, "It is reassuring that no safety concerns were detected in the infants or mothers in this trial, although the number of participants was small."

It should also not be ignored that the trial excluded numerous categories of women including women with high-risk pregnancies, women who conceived through in vitro fertilization, and obese women with a BMI >40 kg/m2.

Finally, and perhaps most concerning of all, the placebo in this trial does not appear to be a true saline placebo. While the study itself does not reveal what the placebo contained, clinicaltrials.gov lists the placebo as a "biological."[9] FDA briefing documents on Pfizer's Abrysvo

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[6] *Supra* note 1, at 9.

[7] www.ncbi.nlm.nih.gov/books/NBK570611 at 1-2.

[8] *Supra* note 1, at 9-10.

[9] https://clinicaltrials.gov/ct2/show/study/NCT04424316?term=Pfizer&cond=RSV+Infection&draw=3&rank=12.

vaccine for use in individuals ages 60 and up indicates that the placebo was "a lyophile match to the vaccine, which consists of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients."[10] Of course, this type of flawed and unscientific study design cannot establish the actual safety profile of a vaccine because the real adverse event rate for a vaccine can only be determined by comparing subjects receiving the vaccine with those receiving an inert placebo. If indeed the same "lyophile match" placebo was used here, this casts even more doubt on the claimed lack of safety signals and sheds new serious doubt on the triumphant claims that the rates of adverse events in the vaccine group were similar to those of the placebo group.

* * *

Concerning adverse events, monitored for an extremely short time, coupled with poor and waning efficacy in this Pfizer-supported study should cause VRBPAC to seriously reconsider making any recommendations regarding this vaccine for healthy, vulnerable mothers and infants.[11]

Very truly yours,

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[10] https://www.fda.gov/media/165623/download.

[11] *Id.* at 13.