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NEWS ANALYSIS

Maternal RSV vaccine: Further analysis is urged on preterm births

A "safety signal" in a similar respiratory syncytial virus (RSV) vaccine has led to trials being stopped and prompted calls for a cautious approach to using the vaccine in pregnant women, reports Hristio Boytchev

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Experts have called for further analysis of trial data and post-approval monitoring of Pfizer's maternal RSV vaccine candidate after GSK's trials of a similar product were halted over a rise in preterm births and neonatal deaths.

An advisory committee from the US Food and Drug Administration (FDA) is set to discuss the vaccine on 18 May[1] as part of a fast tracked priority review, with a decision expected by August.

Pfizer published the results of an interim analysis of its phase 3 trial[2] in April 2023, saying that the vaccine was effective against medically attended severe RSV in children and that no safety concerns were identified.

But the results have raised concerns[3 4] about a possible increase in preterm births, and experts are calling for further analyses of the data and for post-approval monitoring of the vaccine, should the FDA approve it.

GSK halts its trials

In February 2022, GSK halted enrolment and vaccination across three phase 3 trials of its maternal RSV vaccine candidate, citing a safety signal in one of them.[5] It emerged that the concern was about an increased risk of preterm birth in the vaccine arm.[6]

In a document submitted to the FDA, GSK's data showed 238 preterm births out of 3496 (6.8%) in the vaccine arm and 86 out of 1739 (4.9%) in the placebo arm—around one extra preterm birth for every 54 vaccinated mothers.[7] There were 13 neonatal deaths in the vaccine arm and three in the placebo arm.[7]

GSK said it is still investigating the cause of the preterm births and presented preliminary findings in a conference presentation earlier this year.[8]

Ilse Dieussaert, vice president of vaccine development at GSK, said that the increase in neonatal deaths was because of deaths in premature babies and that there was no imbalance of deaths in full term babies. Dieussaert explained that the preterm imbalance was greatest in low and middle income countries (LMIC), which had 9.9% preterm births in the vaccine and 6.3% in the placebo arm. Almost no difference was observed in high income countries.

According to GSK's analysis, the difference in preterm births was highest in LMIC in women who had decided to have different additional vaccines, with 8.2% in the vaccine arm compared with 4.3% in the placebo arm. None other of the factors analysed could explain the safety signal, including SARS-CoV-2 infections, Dieussaert said.

"Similar" vaccine

Pfizer's vaccine is similar to GSK's, although there may be differences in manufacturing, says Cody Meissner, professor of paediatrics and medicine at the Dartmouth Geisel School of Medicine and consultant in the US Centers for Disease Control and Prevention (CDC)'s maternal RSV working group. Both are subunit vaccines using a recombinant RSV F protein of the virus, stabilised in its prefusion state. "I can't really give you an idea as to why one would cause a problem and the other one wouldn't," he said.

After the safety signal in the GSK study came to light, experts have questioned Pfizer over the possibility of an increased risk of preterm birth in its trials. On investor calls in October 2022[9] and March 2023[10] Steve Scala, a pharmaceutical industry research analyst and former pharmacist, described Pfizer's and GSK's vaccines as "Coke and Pepsi" and said he was "wondering why Pfizer can continue and feel comfortable" given that there didn't seem to be a reason for a different incidence of preterm births in the two studies.[10] On both occasions, Pfizer representatives did not give reasons why their vaccine would perform differently to GSK's.

Differences in preterm births are evident in Pfizer's RSV trial. In adverse event tables for its phase 2 study, published in October 2022, Pfizer reported 3 out of 116 (2.6%) premature births in the placebo group and 6 out of 114 (5.3%) in the group that received the vaccine that was chosen as Pfizer's final product.[11]

In a pre-specified interim analysis of Pfizer's related phase 3 trial published in April, 201 babies (5.6%) were born prematurely to vaccinated mothers *v* 169 babies (4.7%) in the placebo group.[12] According to the protocol of the trial, Pfizer was studying preterm birth as an "adverse event of special interest."[12]

Pfizer did not respond when asked about a possible increase in preterm births associated with the vaccine in its two trials, but told The BMJ that "no imbalance of neonatal deaths was observed" in its phase 3 trial.

Calls to monitor Pfizer's results

While the difference in preterm births in the Pfizer trials was not statistically significant, it should be reviewed in light of the signal seen in GSK's trial, experts told *The BMJ*.

"My interpretation of all these data is that there may be a safety signal for preterm births that should be followed up," said Klaus Überla, director of the Virological Institute of the University Hospital Erlangen and member of the RSV working group of the Standing Committee on Vaccination (STIKO), which develops national recommendations for the use of licensed vaccines in Germany.

After a possible approval, the vaccine manufacturers will probably be obliged to monitor a much higher number of pregnancies than were studied in the trials, said Fred Zepp, vice president of the Association of the Scientific Medical Societies in Germany and member of the STIKO RSV working group. (Zepp stressed he was speaking as a researcher and not on behalf of STIKO).

The Pfizer data should be analysed using more sensitive measures such as average birth weight and subgroup analyses to detect possible signals, said a scientist at the US National Institutes of Health who was not authorised to speak with the media.

Meissner predicts that possible adverse effects such as premature births will be "closely monitored" in assessment programs by FDA and CDC. "We need a safe vaccine," he added.

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1 FDA. Vaccines and related biological products advisory committee, May 18 2023 meeting announcement. www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-may-18-2023-meeting-announcement.

2 Kampmann B, Madhi SA, Munjal I, etalMATISSE Study Group. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med* 2023;388:-64. doi: 10.1056/NEJMoa2216480 pmid: 37018474

3 Dave the Knave. Pfizer's RSV vaccine in pregnant women. Sensible Medicine. April 2023. https://sensiblemed.substack.com/p/pfizers-rsv-vaccine-in-pregnant-women

4 Hollander B. A glaring issue with Pfizer's "successful" RSV vaccine. Real Clear Science. 14 April 2023. www.realclearscience.com/2023/04/14/a_glaring_issue_with_pfizers_successful_rsv_vaccine_893746.html.

5 GSK provides further update on phase III RSV maternal vaccine candidate programme. 28February 2022. www.gsk.com/en-gb/media/press-releases/gsk-provides-further-update-on-phase-iii-rsv-maternal-vaccine-candidate-programme.

6 GlaxoSmithKline management presents at 42nd annual Cowen health care conference (Transcript). Seeking Alpha. 2022. https://seekingalpha.com/article/4493526-glaxosmithkline-plc-gsk-management-presents-42nd-annual-cowen-health-care-conference.

7 FDA. GlaxoSmithKline Biologicals SA. Sponsor briefing document vaccines and related biological products advisory committee meeting date: February 28-March 1, 2023. www.fda.gov/media/165621/download#page=42

8 ReSViNET Foundation. Resvinet Conference 2023 Day 2. Youtube. www.youtube.com/watch?v=P45AbqFeYBY&t=28346s.

9 Transcript: Pfizer shareholder/analyst. Market Screener. October 2022. www.marketscreener.com/quote/stock/PFIZER-INC-23365019/news/Transcript-Pfizer-Inc-Shareholder-Analyst-Call-42062169.

10 Pfizer presents at Cowen 43rd annual health care conference. Seeking Alpha. March 2023. https://seekingalpha.com/article/4585306-pfizer-inc-pfe-presents-cowen-43rd-annual-health-care-conference-transcript

11 Pfizer. A phase 2b placebo-controlled, randomized study of a respiratory syncytial virus vaccine in pregnant women. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/results/NCT04032093?view=results.

12 Kampmann B, Madhi SA, Munjal I, etalMATISSE Study Group. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med* 2023;388:-64. doi: 10.1056/NEJMoa2216480 pmid: 37018474