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Concerns over informed consent for pregnant women in Pfizer's RSV vaccine trial

Some experts have criticised Pfizer for not informing pregnant women in its trial of maternal respiratory syncytial virus vaccine that trials of a similar vaccine were halted over a potential risk of preterm birth. Others think that notification would have been premature and caused unnecessary anxiety. Hristio Boytchev reports

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A debate has broken out over whether Pfizer should have told pregnant women participating in its trial of maternal respiratory syncytial virus (RSV) vaccination that a trial of a similar vaccine was halted over a safety signal around preterm birth, *The BMJ* can report. Both GSK and Pfizer were developing recombinant RSV F protein vaccines to inoculate pregnant women and protect their babies against RSV, a major cause of infant death globally.

GSK halted its phase 3 vaccine trial on 28 February 2022 after a safety signal emerged: a possible increased risk of preterm births and neonatal deaths. In the vaccine arm, 6.81% of births were preterm (95% confidence interval 5.99% to 7.69%) compared with 4.95% (3.97% to 6.07%) in the placebo arm. For neonatal deaths, the percentage was 0.37% (0.20% to 0.64%) in the vaccine versus 0.17% (0.04% to 0.50%) in the placebo arm.[1 2] No clear explanation has been found for the increase in preterm births, and experts think that it might be unrelated to the vaccine. GSK told *The BMJ* that the imbalance was observed primarily in low and middle income countries and not consistently after a peak in late 2021,[3] and that it was still investigating the cause of the preterm births but was no longer developing its vaccine.

Pfizer was studying preterm births as an adverse event of special interest in its own phase 3 trial, and a numerical (not statistically significant) imbalance in preterm births has recently emerged in phase 3 data: 5.7% (4.9% to 6.5%) in the vaccine versus 4.7% (4.1% to 5.5%) in the placebo arm, although there are not enough data to understand if there is truly an increased risk or what the cause is.[4 5]

After GSK's trial was halted, opinion was split among clinical trial ethicists and some vaccine researchers over whether Pfizer should have informed all women participating in its trial about the potential risk or updated its consent forms. Some think that only women who had not yet been vaccinated needed to be informed, whereas others think that because there is currently neither convincing evidence nor an explanation for the increased preterm risk, informing expectant mothers would have only caused unnecessary anxiety.

Charles Weijer, bioethics professor at Western University in London, Canada, told *The BMJ* that informing pregnant women in Pfizer's trial about GSK's results would have allowed women who had not yet received the jab to consider whether they still wanted to get it and women who had already received it to seek additional medical advice and follow-up. "Any failure to provide new and potentially important safety information data to trial participants is ethically problematic," Weijer said.

The independent Data and Safety Monitoring Board (DSMB), which reviews and evaluates study data to protect participants' safety and monitor the study's progress, should normally have considered GSK's results and decided if they merited attention, said Stephen Evans, emeritus professor of pharmacoepidemiology at the London School of Hygiene and Tropical Medicine. "For Pfizer, the DSMB should have regularly assessed the benefit-harm balance, both on the data in the trial and whether the GSK results affected that balance. They should not base their decision simply on whether a particular result is 'statistically significant.' These are difficult decisions, and it is why DSMBs are independent of the company,' he told *The BMJ*.

The DSMB for the Pfizer trial didn't answer *The BMJ*'s questions about whether it had considered the GSK results, and two trial investigators told *The BMJ* that they hadn't received any communication from the DSMB regarding the results. Pfizer has also been criticised for a passage in some of its trial consent forms, seen by *The BMJ*, saying that its vaccine candidate was risk-free for the baby; a research ethics expert described this assurance as "misleading" and "irresponsible." Pfizer did not respond to *The BMJ*'s questions on the issue of informed consent.

Safety signals investigated

GSK told *The BMJ* that "immediately" after making the decision to halt its trials over the safety signal, it informed the health authorities and researchers involved in the trial. It also updated its consent forms. Over a year after GSK's trial was halted, *The BMJ* reported in May 2023 that experts had called for further analysis of Pfizer's phase 3 trial data after the slight numerical increase in preterm births was seen.[6] The imbalance was discussed a week later by the US Food and Drug Administration's vaccines and related biological products advisory committee.[7] Ahead of the meeting, the FDA published an analysis showing

that there was no increase in preterm births in high income countries, but there was a numerical increase in upper middle income countries, driven particularly by South Africa.[5]

The committee ultimately advised that Pfizer's maternal RSV candidate was safe, although four of 14 members voted that the data presented by Pfizer were not adequate to support safety after a detailed discussion on the preterm births. Committee member Paul Offit, professor of paediatrics at the Children's Hospital of Philadelphia, said in a meeting that Pfizer's and GSK's vaccines were "almost identical" and so was concerned by GSK's results. Hana El Sahly, professor of molecular virology and microbiology at Baylor College of Medicine and committee chairwoman, said that the signal of increased preterm births connected to the Pfizer vaccine was "significant in the phase 2, in the phase 3, and in a very similar product," adding that failing to design the Pfizer phase 3 study to deliver clarity was a "big missed opportunity."[8]

Regulators have taken different approaches when approving Pfizer's vaccine, which is called Abrysvo. The FDA approved it with conditions, including only giving it to women who are 32-36 weeks pregnant. "Available data are insufficient to establish or exclude a causal relationship between preterm birth and Abrysvo," said a warning included in the prescribing information.[9] "To avoid the potential risk of preterm birth with use of Abrysvo before 32 weeks of gestation, administer Abrysvo as indicated in pregnant individuals at 32 through 36 weeks gestational age." The FDA is requiring Pfizer to conduct postmarketing studies to "assess the signal of serious risk of preterm birth."

Other regulators and national advisory committees, however, such as the European Medicines Agency and the UK's Joint Committee on Vaccination and Immunisation, did not consider a warning around the possible risk of preterm birth or restricting the use of the vaccine to the later weeks of pregnancy necessary in their regions. The Pfizer vaccine is not yet authorised in the UK, and the details of authorisation are not yet clear.

Should trial participants have been informed?

As Pfizer didn't respond to the questions about whether it had informed expectant mothers in its trial about GSK's results, *The BMJ* contacted governmental health authorities in all 18 countries where Pfizer had trial sites, as well as more than 80 trial investigators, and none answered saying that it had. Some confirmed that Pfizer continued to enrol and vaccinate women for months after the news of the potential risk of preterm birth in GSK's vaccine trial was made public.

Clinical trial ethicists and some other experts think that Pfizer should have made pregnant women in its trial aware of the potential preterm risk; some trial investigators and health authorities disagree. "Once the results of the GSK trial on premature births became public, RSV vaccine studies in pregnant women should be updated to include this possible preterm risk," Klaus Überla told *The BMJ*. Überla is director of the Institute of Clinical and Molecular Virology of the University Hospital Erlangen and a member of the RSV working group of the standing committee on vaccination, which develops national recommendations for the use of licensed vaccines in Germany.

"The renewal of informed consent is a must," added Rose Bernabe, professor of research ethics and research integrity at the University of Oslo. She pointed to guidelines from the Council for International Organizations of Medical Sciences, which state: "Researchers must renew the informed consent . . . if new information becomes available that could affect the willingness of participants to continue."[10] The internationally recognised Guideline for Good Clinical Practice contains a similar passage.[11] In its trial publication, Pfizer said that it followed these guidelines.[12]

One trial investigator, speaking to *The BMJ* on the condition of anonymity because they had signed a confidentiality agreement with the company, said that early in 2022 they questioned Pfizer about the potential risk of preterm birth given the similarity between Pfizer's and GSK's products and wanted to know whether Pfizer trial participants could be reassured. "All I got from Pfizer was that their data hadn't shown any increase in risk, no answer to my question," the researcher said. Nothing was communicated regarding whether the DSMB had discussed the matter, they said. A trial investigator from South Africa, also speaking on the condition of anonymity, agreed that participants should have been informed.

But other trial investigators disagree. Beate Kampmann, director of the Centre for Global Health at Charite University Hospital Berlin, one of the lead authors of Pfizer's phase 3 trial publication, and who was responsible for a trial site in the Gambia, told *The BMJ* that GSK's results weren't relevant to her trial participants "as most participants were already in follow-up." She said that the Pfizer vaccine was not the same as the GSK product and that the trial's DSMB "did not raise any concerns." "This was a very location specific and also transient finding, which remains poorly understood," she added. She said that *The BMJ*'s questions on informed consent and possible side effects in the trial amounted to "getting hung up on issues which are not borne out by the analysis and are distorting the benefits this vaccine can bring."

Kampmann did not clarify whether the DSMB had discussed the GSK results, and the DSMB's chair, Flor Munoz, associate professor of paediatrics at Baylor College of Medicine, refused to tell *The BMJ* whether the board had reviewed GSK's results, citing confidentiality agreements.

As the risk was uncertain and the cause of the increase in preterm births still not understood, amending the consent forms was not warranted, said Joop van Gerven, chair of the Dutch Central Committee on Research Involving Human Subjects (CCMO), a national ethics body responsible for the trial. "This would have caused too much uncertainty (without any clinical consequences) for the large number of patients who had already received the vaccine," he told *The BMJ*. The Spanish health ministry shared this view.

"Misleading" consent forms

Pfizer did not disclose in patient consent forms for its phase 3 trial that it was studying preterm birth as an "adverse event of special interest," documents from the US, Canada,[13] the Netherlands, Finland, and New Zealand, obtained by *The BMJ*, show. In addition, some Pfizer trial consent forms seen by *The BMJ* contain contradictory statements, warning of possible "life threatening" effects of the vaccine on the baby while also carrying a passage saying that only the expectant mother is at risk from adverse effects. The consent forms stated: "The risks associated with the study vaccine (RSVpreF or placebo) may be experienced by you, but not your baby, since your baby will not receive the study vaccine or placebo directly."

"Knowing what we know now, the statement in question is irresponsible and, given the benefit of hindsight, is actually factually incorrect," said Bernabe of the University of Oslo. "The statement gives the false sense of security that the fetus or neonate will not be exposed to any risk or inconvenience. Considering the gravity of the risk that this irresponsible statement veils, this misleading

statement should be a ground for questioning the validity of the consent process."

The Dutch national research ethics body, CCMO, admitted that the passage could "potentially cause confusion." Following *The BMJ*'s queries, the Dutch authority alerted Pfizer to possible reader confusion and recommended the passage be adapted, van Gerven, of the CCMO, told *The BMJ*. "However, as it has since emerged that no new participants will be included in the study, making an adjustment . . . is no longer an issue," he said.

Fig 1 | Key dates in maternal RSV vaccine development

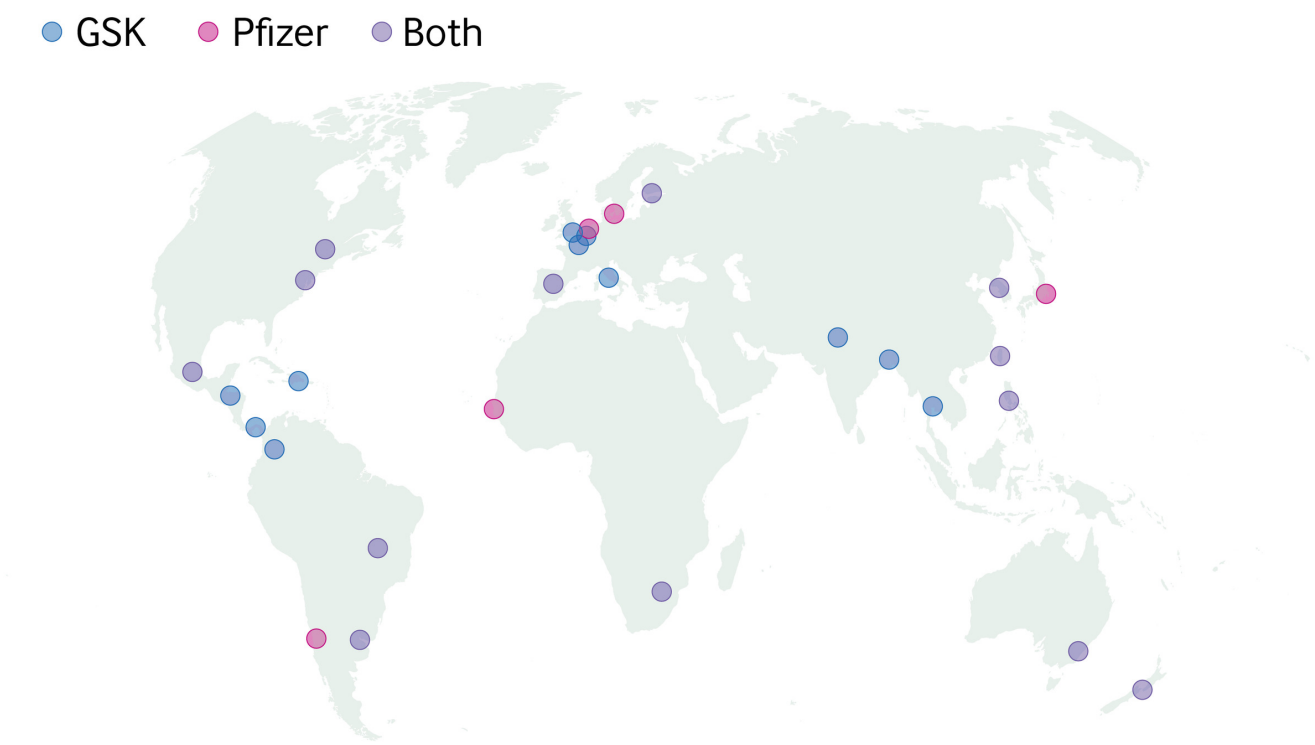

Fig 2 | Maternal RSV vaccine phase 3 locations

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