妊婦用 RS ウイルスワクチン:
アブリスボ試験における主要アウトカム評価に関する懸念

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編集長殿

ファイザー社製 RSV ワクチン、アブリスボ®の試験における妊婦へのインフォームド・コンセントに関する懸念[1]や 2 つの類似した RSV ワクチン間で早産や新生児死亡の有害事象の頻度が異なることへの疑問[2]に加え、私たちは、出生後 24 か月間の先天異常と新生児死亡の割合に不自然な不均衡があり、これが、割付の不均衡を示唆していることを指摘しました[3]。

ファイザー社製母体用 RSV ワクチン（アブリスボ）[4-6]に関して私たちは、もう一つの重大な偏りを発見しました。それは、アウトカム評価に関するものです。

高度（severe）で RSV 陽性の受診下気道感染症（高度 RSV-MA-LRTI）は、RSV 検査が陽性で、以下の徴候の少なくとも 1 つを伴う MA-RTI（受診気道感染）と定義されています[4]：頻呼吸（生後 2 か月未満［生後 60 日未満］では呼吸数 70 回/分以上、生後 2 か月以上 12 か月未満では 60 回/分以上、生後 12 か月以上 24 か月未満では 50 回/分以上）、SpO_2 <93%、その他、より重篤な徴候。

主要報告[4]の結果によると、高度 RSV-MA-LRTI 症例には入院 RSV-RTI よりも軽症の症例も含まれるようです。これは、生後 180 日間で両群を合計すると、高度 RSV-MA-LRTI 症例（「高度」または S）に分類された症例は 81 例、入院 RSV-RTI 症例（「入院」または H）は 63 例あったことによります。

RCT における割り付けが公平で、遮蔽（目隠し）が完全であれば、「入院（H)」／「高度（S)」の比はアブリスボ群（Ha/Sa）とプラセボ群（Hp/Sp）で同程度となり、したがって、1-H/S=(S-H)/S の比も両群で同程度となるはずです。

生後 90 日までの時点では、「高度」症例と「入院」症例の数は両群でよく似ていました（アブリスボ群で「入院」症例数がわずかに多かったが、両群間の差は極めて小さかった)。

MATTISSE 試験[4-6]では、生後 180 日までの「高度」RSV-MA-LRTI が優先的な主要アウトカムとされています。この期間において、プラセボ群では「高度」と分類されたが「入院」に至らなかった症例数（Sp-Hp）は 18 件（62-44）であったのに対し、アブリスボ群では「高度」と分類されたが「入院」に至らなかった症例数（Sa-Ha）は 0 件（19-19）でした。

アブリスボ群の 0/19 の割合とプラセボ群の 18/62 の割合を比較したところ、オッズ比は 0、フィッシャーの正確検定を用いて算出した 95%信頼区間は 0-0.59、p 値は 0.0048 となり、割合の差は統計学的に有意でした。

以上、第 3 相 RCT においては、高度 RSV-MA-LRTI が主要評価項目として公平に評価されなかった可能性が高く、アブリスボ群において生後 180 日までに報告された症例数が少なすぎるため、アブリスボの有効性が過大評価された可能性が高いと考えます。

したがって、「高度 RSV 陽性 MA-LRTI」は主要評価項目として信頼性が低いといえます。

先天異常と生後 24 か月間の新生児～乳幼児死亡率の割合の不自然な不均衡は、割りつけの不均衡を示唆するものですが、それに加えて今回の我々の意見で指摘した遮蔽不全を示唆するデータは、ファイザー社製ワクチン「アブリスボ」の第 3 相試験の信頼性を著しく損なうものと考えます。

臨床試験報告書のオリジナルデータを用いた検証が必要です。

参考文献（原文の後に示します）

原文は以下のとおりです（一部修正済み、修正箇所は文末に表示しました）。。

Re: Maternal RSV vaccine: Concerns Regarding Primary Endpoint Assessment in Pfizer's RSV Vaccine Trial

Dear Editor

In addition to the concerns regarding informed consent for pregnant women in Pfizer's RSV vaccine trial [1] and questions about the differences in the adverse outcomes in preterm birth and neonatal death between two similar RSV vaccines [2] we pointed out an unnatural imbalance in the proportions of the congenital anomalies and neonatal deaths during 24 months after birth which suggested an imbalance in allocation [3] .

We found another potentially serious bias regarding the outcome assessment in the Pfizer's maternal RSV vaccine (Abrysvo) [4-6].

Severe RSV-positive medically-attended lower respiratory tract infection (severe RSV-MA-LRTI) is defined as an MA-RTI with RSV-positive test result and with at least one of the following signs: fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for 2–<12 months of age, or ≥50 bpm for 12–24 months of age), SpO_2 <93% or other severer sings [4]. According to the results of the report [4], severe RSV-MA-LRTI cases appear to include milder cases than hospitalised RSV-RTI, because there were 81 cases who were classified as the severe RSV-MA-LRTI cases ("severe" or S) and 63 hospitalised RSV-RTI cases ("hospitalised" or H) among both groups during the 180 days after birth. If allocation in an RCT is fair and masking is complete, the ratio of "hospitalised (H)"/"severe (S)" should be similar in the Abrysvo group (Ha/Sa) and in the placebo group (Hp/Sp), and therefore the ratio 1-H/S=(S-H)/S should be similar in both groups.

Up to 90 days after birth, the number of "severe" and "hospitalised" cases were very similar in both groups (the difference between the two groups was extremely small, even with slightly more "hospitalised" cases in the Abrysvo group).

In the MATTISSE trial [4-6], "severe" RSV-MA-LRTI by 180 days after birth is considered the preferential primary outcome. In this time windows, the number of cases classified as "severe" but not "hospitalised" (Sp-Hp) was 18 (62-44) in the placebo group, while that as "severe" but not "hospitalised" (Sa-Ha) was 0 (19-19) in the Abrysvo group.

By comparing the proportion 0/19 in the Abrysvo group with the proportion 18/62 in the placebo group, the odds ratio was calculated as 0, the 95% confidence interval, calculated using Fisher's exact test was 0 to 0.59, and the p-value was 0.0048, indicating significant difference.

It is highly likely that the severe RSV-MA-LRTI in the phase 3 RCT were not evaluated fairly and were reported too few as the primary outcome in the Abrysvo group by 180 days after birth, leading to overestimation of efficacy of Abrysvo. Therefore, the "severe RSV-positive MA-LRTI" is unreliable as the primary outcome.

In addition to the unnatural imbalance in the proportion of the congenital anomalies and neonatal mortality during 24 months after birth which suggested allocation imbalance, these data in this response suggesting masking failure significantly undermines the credibility of the phase 3 trial of the Pfizer vaccine "Abrysvo".

Verification using original data from the clinical study reports is necessary.

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References

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2) Boytchev H. Maternal RSV vaccine: Further analysis is urged on preterm births B*MJ* 2023 10 May 2023;381:p1021 doi: https://doi.org/10.1136/bmj.p1021
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https://www.bmj.com/content/381/bmj.p1021/rr-1
4) Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. NEJM. 2023; 388: 1451-1464. PMID: 37018474. (with protocol and supplementary appendix)
5) Madhi SA, Kampmann B, Simoes EAF, et al. Preterm Birth Frequency and Associated Outcomes From the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Trial of the Bivalent Respiratory Syncytial Virus Prefusion F Protein Vaccine Obstet Gynecol 2025; 145: 147-156. PMID: 39746206 (with supplementary appendix).
6) Simoes EAF, Pahud BA, Madhi SA, et al. Efficacy, Safety, and Immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Respiratory Syncytial Virus Prefusion F Protein Vaccine Trial. Obstet Gynecol 2025; 145: 157-167. PMID: 39746212 (with supplementary appendix).

Re: Maternal RSV vaccine: Correction of Concerns Regarding Primary Endpoint Assessment in Pfizer's RSV Vaccine Trial

Dear Editor

We would like to correct the first sentence in the third paragraph from the bottom of our second response:

It is highly likely that the severe RSV-MA-LRTI in the phase 3 RCT were not evaluated fairly as the primary outcomes.

is corrected as follows：

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It is highly likely that the severe RSV-MA-LRTI in the phase 3 RCT were not evaluated fairly and were reported too few as the primary outcome in the Abrysvo group by 180 days after birth, leading to overestimation of efficacy of Abrysvo.

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Competing interests: No competing interests

AI use: None declared