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Letter to the editor RE: Berendsen et al., 2016 'Non-specific Effects of Vaccines and Stunting: Timing May Be Essential'

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We read with great interest the article by Berendsen et al. [1] In this article, the authors aimed to evaluate the effect of timing of infant vaccination with Bacillus Calmette–Guérin (BCG), DTP1, and measles vaccine (MV) on stunting, among other outcomes. For this purpose, the authors retrospectively used secondary survey data on 368450 children from 33 Sub-Saharan African countries and, using logistic regression analyses, cross-sectionally performed mainly two types of analyses: 1. estimation of the odds of stunting in children with a past BCG, DTP1, and MV vaccination (separately) in comparison to unvaccinated children in overall and stratifying by the timing of vaccination 2. estimation of the odds of stunting in relation to a continuous variable for the timing of past vaccination with BCG, DTP1, and MV (separately).

Stunting is defined as the impaired growth and development of children indicated by a considerably decreased height-for-age. Stunting has serious long-term effects on morbidity, mortality, and psycho-cognitive and social development. The condition is particularly important in Sub-Saharan Africa where the prevalence of stunting is alarmingly high.

The findings of Berendsen et al. included lower odds of stunting in children who had a BCG vaccination early in life in comparison to children without BCG vaccination. However, the authors also reported paradoxically increased odds of stunting with BCG, DTP1, and MV vaccination later in infancy. Based on their study, the authors suggested that the timing of vaccination during infancy could sensitively have serious health implications with opposing effects on stunting when BCG vaccination was given during the first month of life (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.89 to 0.94) compared to when given during the second or third month of life (1.05; 1.01 to 1.09) or when given later in infancy (1.64; 1.53 to 1.76), in reference to no BCG vaccination. The authors reported similar results with early and delayed vaccination using DTP1 and MV vaccines.

These considerably deleterious effects of delayed BCG, DTP1, and MV vaccination could be of enormous clinical importance. For instance, the study findings challenge the decision to give BCG, DTP1, or MV vaccination to infants who missed the recommended early vaccination while it is well established that these vaccines could be lifesaving in regions where diseases such as tuberculosis and diphtheria are prevalent. Another important implication of the findings is the substantiation of scepticism regarding the non-specific long-term effects of vaccines which might bolster general vaccination hesitancy: a subject of particular relevance during these times of coronavirus disease 2019 pandemic.

Nevertheless, we are concerned about the internal validity of these findings as we suspect bias in relation to two factors: a. neonatal and serious infancy infections b. parental adverse childhood experiences, notably neglect. The confounding is due to the likely association of these two factors with both the delay in vaccination and the risk of stunting. While perceived as temporary contraindications to vaccination and justifying its delay, neonatal and serious infancy infections are known for their implications on development and growth. Also, adverse and neglectful parenting could cause both a postponement of vaccination and increased odds of stunting and would not be necessarily proxied by the household's socioeconomic status.

The authors adjusted for a range of covariates including covariates at the children individual level, covariates at the household level, and covariates at a regional level, but not for the occurrence and timing of infancy infections or for adverse parenting. While this scenario might resemble the classic case of confounding [2], the systematic error suspected in the main study analysis examining previously vaccinated vs unvaccinated stratified by timing of vaccination could be of type selective survivor bias [3]. Children with late infancy vaccination could differentially be a selected population of those who missed early infancy vaccination because of parental neglect or a contraindication to vaccination such as infection. This bias would apply to all three studied vaccines, as well as another outcome evaluated by the authors (haemoglobin concentration). Data directly measuring these factors would likely be missing from the database, but neglect and a

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contraindication to vaccination could be accounted for by proper adjustment for indirect indicators such as the timing of other vaccinations and the child's status of nutrition.

Contributors

Both authors conceived and co-wrote this Letter to the editor.

Declaration of Competing Interest

Mounir Ould Setti is employed as an epidemiologist by IQVIA, a contract research organisation that offers services to multiple clients from the biomedical industry. Nevertheless, the writing of this Letter was not initiated by IQVIA, nor did IQVIA fund it. Otherwise, the authors declare no conflicts of interest.

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