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Optimising the vaccine strategy of BCG, ChAdOx185A, and MVA85A for tuberculosis control

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We write in response to the comment by Wenping Gong and Jingli Du[1] about our published research article on safety and immunogenicity of ChAdOx1 85A prime followed by MVA85A boost compared with BCG revaccination among Ugandan adolescents who received BCG at birth: a randomised, open-label trial.[2]

We appreciate the comment's recognition of our efforts towards identifying a better protective vaccine regimen for the highly transmissible pulmonary tuberculosis which is endemic in tropical regions such as Uganda and affects more adult men and women than children.[3]

However, the comment states that the major limitation of our study design is that we did not use the BCG-ChAdOx1 85A-MVA85A immunisation strategy.[1] This is incorrect. We agree that a combination of BCG-ChAdOx1 85A-MVA85A vaccination regimen has been shown, in an animal model, to induce superior immunogenicity and better *Mycobacterium tuberculosis* (MTB) control than when vaccines were administered alone.[4,5] Our study in fact followed a similar BCG-ChAdOx1 85A-MVA85A vaccination approach, as highlighted in the introduction to our paper: our participants were from a birth cohort and those recruited to this trial had all been documented to receive vaccination at birth with BCG Russia, as detailed in our methods.[2] It is of note that the development of a BCG scar depends on several factors including the needle used, injection technique and BCG strain administered. The scar prevalence at recruitment to our trial aligns with our data on scarring with this strain in this cohort.[6] It has been shown that neonatal BCG vaccine efficacy wanes between ages 10 to 15 years.[7] The median age of our adolescent participants at recruitment to the randomised phase 2a trial was 15 years (IQR 14-16),[2] which is the optimal age to administer and to test the immunogenicity and efficacy of tuberculosis vaccine regimens designed to boost neonatal BCG vaccine responses.

Gong and Du made an inference based on our early secretory antigenic target 6 (ESAT-6) and the 10-kDa culture filtrate protein (CFP-10) ELISpot (IFN-γ release assay-IGRA) assay results regarding latent tuberculosis infection (LTBI) acquisition during the study. They state that, "combined booster most likely has a higher efficacy at preventing LTBI conversion than a single ChAdOx1 85A booster."[1] Given the small sample size, our study was not powered to

compare the efficacy of ChAdOx1 85A alone with ChAdOx1 85A-MVA85A and BCG revaccination at preventing LTBI acquisition. Moreover, most of the participants who converted their ESAT-6/CFP-10 ELISpot response reverted by the next clinic visit. Only 4 participants remained IGRA positive throughout the study.[2] None of our participants who converted developed signs or symptoms of active tuberculosis.[2] Given that false positive conversions with IGRAs have been observed among 563 health-care workers undergoing occupational tuberculosis screening at four health-care institutions in the USA, a low tuberculosis incidence area with an average tuberculosis case rate that ranged from 4 to 9 per 100 000 persons,[8] it is not certain that our participants acquired LTBI during the study.

Our study shows that ChAdOx1 85A-MVA85A induces superior immunogenicity to Ag85A compared with BCG revaccination.[2] Purified protein derivative-specific responses were comparable between ChAdOx1 85A-MVA85A and BCG revaccination trial arms.[2] ChAdOx1 85A-MVA85A induced similar immune responses in Ugandan and UK populations.[2] We agree with the authors on the need for further development of booster vaccines against tuberculosis and to assess their immunogenicity and efficacy in large clinical trials in endemic countries.

We declare no competing interests.

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