TITLE:

Live attenuated oral vaccine, age and anti-Vi antibody status at baseline significantly affect attack rate in a human *Salmonella* Typhi challenge model

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ABSTRACT TEXT:

BACKGROUND

Salmonella Typhi infection remains a neglected cause of non-specific fever and mortality. Currently available vaccines are limited in efficacy, duration of protection and suitability for young children, while factors correlating with protection from infection remain unclear.

METHODS

Volunteers aged between 18 and 60 years were randomly allocated to receive M01ZH09 or placebo (double-blind), or Ty21a. Twenty-eight days after vaccination, participants were challenged with *S.* Typhi (Quailes strain) suspended in sodium bicarbonate solution. Participants were observed for 2 weeks, with regular clinical assessment and sample collection. Participants

reaching pre-defined endpoints for typhoid diagnosis (temperature ≥38°C for ≥12hours and/or blood culturing *S.* Typhi) were initiated on antibiotic and used to calculate vaccine efficacy.

RESULTS

91/99 participants completed vaccination and challenge. M01ZH09 was highly immunogenic generating significant increases in anti-LPS and H ASC and antibody titres surmounting those seen in Ty21a vaccinated participants.

Participants were challenged with 1.46 - 2.66x10^4 CFU *S.* Typhi. Of participants receiving placebo, M01ZH09 and Ty21a, typhoid was diagnosed in 66.7, 58.1 and 43.3% respectively, demonstrating protective efficacy of 13% for M01ZH09 and 35% for Ty21a. M01ZH09 recipients demonstrated delayed infection onset, milder symptom profile, fewer positive blood cultures overall and fewer positive stool cultures prior to typhoid diagnosis.

In further post-hoc, multivariate analyses, increasing participant age and baseline anti-Vi antibody status were found to be additional significant factors affecting susceptibility to typhoid infection.

CONCLUSION

Taking advancing age and baseline anti-Vi antibody status into account, receipt of either a single dose of M01ZH09 or 3-doses of Ty21a resulted in a ~2fold reduction in typhoid risk during the challenge period.