Assessing serum anti-rotavirus immunoglobulin A as a correlate of vaccine-induced protection against rotavirus gastroenteritis in high and low child mortality settings: analysis of pooled individual-level data from nine clinical trials

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Background
A correlate of protection would facilitate rapid and efficient assessment of modified rotavirus vaccine strategies and the next generation of rotavirus vaccines. We aimed to quantify a threshold of post-vaccine serum anti-rotavirus immunoglobulin A (IgA) antibody units that serves as an individual-level immune correlate of protection against rotavirus gastroenteritis among vaccinated infants across child mortality settings.

Method
Individual-level data on 5,074 infants enrolled in nine GlaxoSmithKline Rotarix phase II and III clinical trials from 16 countries were pooled. Cox proportional hazard models were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) describing the relationship between a series of IgA thresholds and the occurrence of mild/moderate or severe rotavirus gastroenteritis up to 1 year of age.

Results
Seroconversion (serum IgA ≥20 U/mL) conferred substantial protection against mild/moderate and severe rotavirus gastroenteritis. Among infants in low child mortality settings, seroconversion provided near perfect protection against severe rotavirus gastroenteritis (HR=0.04, 95% CI=0.01, 0.32). In high child mortality settings, seroconversion reduced the risk of severe rotavirus gastroenteritis by 52% (HR=0.48, 95% CI=0.26, 0.90). As IgA threshold increased, the HR comparing the rate of gastroenteritis among those above that threshold to seronegative infants generally decreased. A given IgA threshold provided consistently higher protection in low child mortality settings compared to high child mortality settings and for more severe disease compared to mild/moderate disease.

Conclusion
Serum IgA is a valuable, though imperfect, correlate of vaccine-induced protection against rotavirus gastroenteritis across settings. Serum IgA alone may be insufficient to accurately predict an infant's risk of rotavirus gastroenteritis, however, seroconversion provides an informative threshold for assessing rotavirus vaccine performance.