Efficacy of live oral rotavirus vaccines

Andrew Clark and colleagues[1] present important data from meta-regression of the results of 50 randomised controlled trials that show a lower and more rapid waning efficacy of rotavirus vaccines (mainly Rotarix and RotaTeq) in high-mortality settings (Africa and south Asia) than in low-mortality settings (Europe, USA, Japan, Singapore, Hong Kong, and Taiwan).[1] Globally, rotavirus is the most common diarrhoeal pathogen among infants and young children, and rotavirus infection causes approximately 199 000 deaths according to the Global Burden of Disease Study 2015, with over 90% of deaths occurring in developing countries in Asia and Africa.[2,3] The reasons for this geographical variation in rotavirus vaccine efficacy are not fully understood. The authors interpret this finding in terms of immunogenicity and natural infection.[1]

We propose another possible interpretation. In-vitro studies have shown that the most common rotaviruses recognise human histo-blood group antigens (HBGAs) in a P genotype-dependent manner.[4] HBGAs are carbohydrates and include ABO, secretor, and Lewis antigens. There is marked difference in HBGA phenotypes between ethnic groups. For instance, in a population-based study of two independent cohorts, Nordgren and colleagues[5] found a 4–6% prevalence of the Lewis-negative phenotype in white populations, yet this phenotype reached over 30% prevalence in certain African and Latin American populations. Importantly, Nordgren and colleagues[5] reported that P[8] rotaviruses exclusively infected Lewis-positive children, and P[6] rotaviruses mainly infected Lewis-negative children, which might account for reduced vaccine efficacy in Africa. Thus, it is reasonable to speculate that different HBGA phenotypes might hold the key to susceptibility to certain rotavirus P genotypes. Further clarity on this matter is of clinical and public health importance for the optimal selection of rotavirus vaccines for infants and young children.

We declare no competing interests.

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1 Clark A, van Zandvoort K, Flasche S, et al. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. *Lancet Infect Dis* 2019; **19:** 717–27.
2 GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017; **17:** 909–48.
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Culture-negative cryptococcal meningitis

We read with interest the Article by Mark W Tenforde and colleagues[1] describing clinical and laboratory predictors of mortality in adult patients with meningitis in Botswana. Using a nationwide patient information system, the authors observed high mortality and ongoing contributions of HIV co-infection on meningitis prevalence over 12 years. We applaud the systematic categorisation of patients included in the analyses, which provides strong justification for the development of improved diagnostics for meningitis in Africa. This strength is conspicuously pertinent to cases of culture-negative meningitis, and the high mortality observed in this group caught our attention.

As discussed in the Article and Comment,[2] the high mortality observed in patients with culture-negative meningitis is probably a result of missed diagnoses. This interpretation would seem most apparent regarding tuberculous meningitis, given the infrequent use of mycobacterial cultures and low-sensitivity of acid-fast bacteria microscopy, which were the only tuberculosis tests available during the study. Cryptococcal antigen (CrAg) testing was also not routinely available during the study period, which might have resulted in missed cases of cryptococcal meningitis, although the authors postulate that standard assessment with India ink microscopy and fungal cultures was likely to have detected most cases. We offer an additional possible explanation of missed diagnoses in HIV-associated cryptococcosis: culture-negative cryptococcal meningitis.

In a large trial of Ugandan adults with a first-episode of HIV-associated cryptococcal meningitis, nearly 10% (64/703) of patients presented with a positive CSF CrAg, but with sterile CSF cultures.[3] In this population, we noted a 10-week mortality similar to that of patients with higher initial fungal burdens (appendix). Patients with sterile cultures in this cohort were more likely to be receiving antiretroviral therapy at diagnosis than were those with positive CSF cultures (75% *vs* 44%; p<0·01), highlighting the high mortality in patients with cryptococcal meningitis even with improved access to antiretroviral therapy.

Additionally, we previously described another sub-population of individuals with advanced HIV and cryptococcosis presenting with positive serum CrAg and signs of meningitis despite negative CSF CrAg and culture.[4] All other diagnostic work-up on CSF,

For the **Global Burden of Disease Study 2015** see https://www.thelancet.com/gbd/2015

See **Online** for appendix