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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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

including multiplex PCR, bacterial and mycobacterial cultures, and Xpert MTB/RIF were negative. We suggested that cryptococcal antigenaemia with meningitis symptoms is most consistent with early cryptococcal meningitis.

Given the high prevalence of cryptococcal meningitis in Botswana and results from other studies,[5] culture-negative cryptococcosis might be an important contributor to undiagnosed meningitis. Better characterisation of these poorly described populations is warranted to inform better management and improve mortality.

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For more on **FIBRE** see https://www.lshtm.ac.uk/research/centres-projects-groups/fiebre

Typhoid Vi-conjugate vaccine for outbreak control in Zimbabwe

Joe Bilcke and colleagues[1] investigated the cost-effectiveness of alternative delivery strategies for typhoid Vi-conjugate vaccine (TCV) in each of the 54 countries eligible for financial support from Gavi, the Vaccine Alliance. In settings with a high incidence of *Salmonella enterica* serotype Typhi (S Typhi), routine vaccination of infants and a catch-up campaign for children younger than 15 years seems to be a cost-effective approach and could reduce the number of typhoid cases in Zimbabwe by 68% over the next 10 years.

Zimbabwe carried out a mass TCV vaccination campaign in February to March, 2019, funded by Gavi, that targeted children aged between 6 months and 15 years in communities affected by an ongoing typhoid outbreak.[2] It was the first time TCV was used in Africa and the first vaccination campaign in response to a typhoid outbreak in the continent. Outbreaks of cholera and typhoid in Zimbabwe result from a lack of investment in and management of the country's water and sanitation infrastructure and health-care system.[3] Additionally, low availability of diagnostics and drugs, brain drain (emigration of highly qualified individuals from a country), prohibitive user fees in health facilities, and strikes by medical personnel have contributed to the most recent outbreak of typhoid.

FIEBRE, a multicountry study, has been enrolling adults and children who present with fever at health facilities in Harare, Zimbabwe, since June, 2018, to investigate the causes of fever in sub-Saharan Africa and southeast Asia. As part of the study, multiple diagnostic investigations have been done, inclu-ding automated blood cultures, bacterial identification, and drug susceptibility testing. S Typhi has been isolated from 23 (17%) of 133 blood cultures from children and 38 (21%) of 183 blood cultures from adults. Of the 61 S Typhi isolates, 54 (89%) were multidrug resistant and 49 (80%) displayed diminished fluoroquinolone susceptibility.

3 months after the vaccination campaign, we observed a sharp decrease in one of the worst affected communities in the proportion of confirmed and suspected typhoid cases among children, but not among adults. In this community, 23 (21%) of 109 blood cultures from children were positive for S Typhi before vaccination compared with none of 24 after vaccination. By contrast, 18 (15%) of 117 blood cultures from adults were positive for S Typhi before vaccination compared with 20 (30%) of 66 after vaccination.

Although the TCV vaccination campaign seems highly effective in reducing typhoid incidence among children, a more comprehensive approach—including vaccination of adults and water, sanitation, and hygiene interventions—will be needed to halt typhoid outbreaks.

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Value of observational data for multidrug-resistant tuberculosis

In their Correspondence, Ibrahim Abubakar and colleagues[1] highlighted the crucial role of explanatory and