Improving the performance of oral rotavirus vaccines

Oral rotavirus vaccines have significantly improved outcomes in high-income countries, where emergency room visits and hospitalisations (ie, admission to hospital) have decreased by over a half from the prevaccine era. These vaccines showed an effectiveness of 84% (range 19–97%; Rotarix), and 90% (64–100%; Rotateq). In these high-income settings, the epidemiology of paediatric diarrhoeal disease has changed, with noroviruses becoming the most common pathogens following the introduction of rotavirus vaccines.2

However, the issue is more complex in low-income and middle-income countries (LMICs), with lower vaccine effectiveness and a continued predominance of rotavirus as a cause of acute diarrhoeal disease even after the vaccine introduction.3 These data make the recommendation of rotavirus vaccines challenging for policy makers, particularly in the context of competing priority vaccines, such as the pneumococcal and human papillomavirus vaccines.4,5 Added to the lower effectiveness, the reported serious side-effect of intussusception, which can result in mortality in children in LMICs, make extended analyses—which consider alternative scenarios that potentially improve benefit and reduce risk—essential.

In 2012, a model based mainly on WHO–UNICEF coverage surveys in 2010 and vaccine performance derived from efficacy trials and limited effectiveness data from Latin America showed that removing age restrictions for rotavirus vaccination would avert an additional 47–200 rotavirus deaths (95% CI 18 700–63 700) and cause an additional 294 (161–471) intussusception deaths.6 In The Lancet Global Health, Andrew Clark and colleagues7 have presented a modelling analysis restricted to 135 LMICs, where deaths are expected for both rotavirus acute gastroenteritis and intussusception, and considers a wider range of potential immunisation schedules, including neonatal and booster doses.

Globally, rotavirus gastroenteritis mortality estimates have declined significantly in the past two decades, probably reflecting better diarrhoeal disease control measures and increased access to care.8 The reduction in deaths attributable to rotavirus is reflected in this analysis with the number of deaths prevented by an age-unrestricted schedule estimated to be about 12 000, about a quarter of the prediction in 2012, but the incremental benefit risk ratio (148:1) continues to be very similar to the previous estimate of 154:1. These data support the WHO recommendation of removal of the age restriction on immunisation. Although WHO’s recommendation states that the wider age range should be considered in countries where the potential benefit exceeds the risk, based on the analysis, the removal of age restriction is applicable to most countries. Nonetheless, which safety data could result in a labelling change removing the age restriction by manufacturers is unclear. Discussions with regulators and agencies such as WHO and UNICEF might be helpful in deciding whether an effort should be made to collate such data.

Given that the outcome is mortality, it is not surprising that the model was sensitive to access to treatment. Mortality estimates in infants in LMICs should be derived from at least verbal autopsy data, but the symptoms of intussusception and the progression to a fatal outcome, which is likely to be over several days, make verbal autopsy in LMICs an uncertain source of fatality rates outside of health-care facilities. The model estimated 14 500 intussusception deaths in 135 LMICs, but the paucity of primary data from many of these countries and the limited measurement of treatment use for intussusception makes it necessary to use assumptions which might not reflect individual country rates. African data from 2018 indicate that rotavirus vaccination is not associated with increased risk of intussusception,8 so it is feasible that the risk estimates of intussusception that derive from high-income, low-mortality settings might not hold for settings where vaccine effectiveness is lower.

For 14 countries, the benefit–risk ratio was statistically significantly lower when children were vaccinated without age restriction. In several of these countries, estimates of acute gastroenteritis and on intussusception appear to derive only from models, and it would be valuable to explore the drivers of high risk.

Neonatal and booster dose schedules have only been tried in a limited number of efficacy trials, but the modelled estimates indicate a more favourable benefit–risk ratio with early delivery of vaccines, and an unaltered benefit–risk ratio but decreased rotavirus
gastroenteritis with a booster dose. Overall, the findings indicate that children will derive benefit from receiving rotavirus vaccines at any age and from alternate rotavirus vaccination schedules. Unfortunately, the settings where there is potential for increased benefit from alternate schedules, are also those where it is challenging to change schedules once vaccines have been introduced, based solely on modelled estimates. India has extended the age of administration of the first dose to 12 months,10 which might, therefore, be an opportunity to gather detailed data on age of administration and the potential effect of an expanded window on vaccine safety and effectiveness.

Rotavirus vaccines have decreased disease and death wherever they have been used, but further benefits are possible through schedule changes. Lacunae in safety and real-world effectiveness data should be addressed to ensure that these benefits are realised.

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