Rotavirus Vaccines in China
Improvement Still Required
Carl D. Kirkwood, PhD; A. Duncan Steele, PhD

It is well recognized that rotavirus vaccines have had an enormous impact in improving child health morbidity and reducing diarrhea-associated mortality in every setting evaluated when introduced into the national immunization programs. Three rotavirus vaccines have now obtained World Health Organization (WHO) prequalification, ROTARIX (GlaxoSmithKline), RotaTeq (Merck), and ROTAVAC (Bharat Biotech), thus enabling their procurement by the United Nations Children's Fund (UNICEF) through Gavi, the Vaccine Alliance. The 2 multinational vaccines prequalified in 2006 (ROTARIX and RotaTeq) are included in the national immunization programs or in phased subnational introductions in 95 countries across the globe. Substantial reductions in diarrhea-associated deaths and hospitalizations have been recorded from multiple countries in Africa, the Americas, and Europe. On the other hand, ROTAVAC is an indigenous, naturally attenuated monovalent G9P[11] rotavirus strain isolated at the All India Institute of Medicine and developed by Bharat Biotech with support from the local Department of Biotechnology, the Indo-US Vaccine Action Program, and PATH. ROTAVAC was licensed by the Drugs Controller General of India in 2015 and has been implemented in a staged introduction plan in India, where implementation first occurred in 4 states in 2016 and in an additional 5 states in 2017; Uttar Pradesh, India, is predicted to introduce ROTAVAC in 2018, thus providing rotavirus vaccination to almost 50% of the birth cohort. This vaccine achieved WHO prequalification in January 2018, enabling global use of the vaccine in other developing countries through Gavi-funded support.

As of mid-2018, 3 additional rotavirus vaccines have been licensed locally by national regulatory agencies. In Vietnam, Rotavin (POLYVAC), derived from a human G1P[8] strain, was licensed for use in 2012 based on a phase 2 immunogenicity study and is currently available in the private market. In India, the Serum Institute of India obtained Drugs Controller General of India approval for the licensure of their pentavalent bovine-human reassortant rotavirus vaccine, ROTASIIL, in 2017, following successful completion of 2 large phase 3 efficacy studies in India and Africa. The government of India has implemented this vaccine in Jarkhland in 2018. The third nationally licensed rotavirus vaccine is the Lanzhou lamb rotavirus (LLR) vaccine developed by Lanzhou Institute of Biological Products in China. This vaccine was licensed in 2000 and has been available on the Chinese private market with an estimated 60 million doses provided. A large case-control effectiveness study reported the LLR vaccine effectiveness at 35% against rotavirus gastroenteritis and 53% against moderate to severe diarrhea.

The study by Fu and colleagues provides a population-based analysis of LLR vaccination coverage and its association with rotavirus gastroenteritis using several data sets from Guangzhou, China, from May 2007 to April 2016. Unfortunately, rotavirus vaccination is not included in China's national immunization program, resulting in low coverage rates due to only private market use. The recommended schedule for LLR vaccination is as a single oral dose annually to infants 2 months to 3 years of age, and in Guangzhou the coverage rates ranged from 6.8% to 28.6% among 12 districts studied between 2009 and 2011. The vaccine costs approximately $24 per dose based on national tariffs.

Importantly, despite the low vaccination coverage rates, districts with higher vaccination levels (>20%) were associated with a lower incidence of rotavirus gastroenteritis compared with districts that had lower coverage (<14%). Vaccination was associated with a 32.4% reduced incidence rate.
ratio in areas of higher vaccination coverage among children younger than 4 years. However, no real impact on the overall rotavirus rates was observed, likely owing to the low vaccination coverage. Using rotavirus gastroenteritis and vaccination data collected during 9 seasons, the authors also reported a 4-month increase in median age at disease onset. This trend has been observed in other settings, but it is more difficult to interpret in this study because of the overall low coverage, the differences in immunization schedule patterns, and the likely socioeconomic differentiation of the children receiving the vaccine through parental influence rather than through the national immunization program.

The data do not mirror the often dramatic reductions in rotavirus-associated gastroenteritis observed in many countries in which rotavirus vaccination is included in national immunization programs (eg, Brazil, Mexico, United States, Belgium, Australia), highlighted in the systematic review of the first decade of postlicensure studies, which reported a 45% to 90% decline in rotavirus-associated hospitalizations among children younger than 5 years. This review also demonstrated that lower vaccine effectiveness occurred in countries with a higher level of child mortality compared with countries with low child mortality. However, the study confirmed that both ROTARIX and RotaTeq are effective against rotavirus gastroenteritis across a range of mortality settings, providing additional evidence for the WHO recommendation that all countries introduce rotavirus vaccination into their national immunization program.

China has a large birth cohort of approximately 16 million live births per year. Furthermore, the proportion of rotavirus-associated diarrhea resulting in hospitalization is high, with figures from 30% to 50% reported. The burden of rotavirus gastroenteritis in China is thus enormous and demonstrates that there would be significant health benefits as well as health cost savings if a national rotavirus immunization schedule was implemented. Several studies have demonstrated that a rotavirus vaccination program is highly cost-effective using the LLR vaccine as well as ROTARIX and RotaTeq, both of which have had clinical trials conducted in China. Interestingly, the RotaTeq vaccine showed 79% efficacy against moderate to severe rotavirus gastroenteritis.

The study by Fu and colleagues reinforces the need and benefit of a universal immunization program with timely vaccine administration, similar to that recommended by WHO, to ensure maximum benefits with the first dose as soon as possible. Despite the well-characterized disease burden and the remarkable impact of rotavirus vaccination, vaccine introduction has been extremely slow across Asia. An analysis by Burnett and colleagues highlights an estimated reduction of nearly 50% in rotavirus-associated hospitalizations and a 40% reduction in rotavirus-associated deaths in Asia if rotavirus vaccines were more widely used in this region. Rotavirus vaccine implementation may have turned an important corner in Asia. India has commenced a staged rollout from 2016. Pakistan introduced rotavirus vaccine in several districts in Punjab in January 2017, and Bangladesh was approved for Gavi-supported introduction in 2018.

The data presented here provide a sense of hope that continued rotavirus vaccine use and improved uptake will lead to improved child health across China. China's State Council's new guidelines for the development, management, and recommendation of vaccines for use will hopefully lead to a strengthening of China's Expanded Program on Immunization system so that immunization, including rotavirus vaccination, is at the forefront to protect children from vaccine-preventable diseases.
REFERENCES


