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Rotavirus vaccine safe, modestly efficacious in Phase III trial

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Children being treated for diarrhoea at a government hospital in Bhubaneswar. India has the most rotavirus deaths in the world. *The Hindu Photo Library*

A Phase III randomised, double-blind, placebo-controlled trial of 116E rotavirus vaccine undertaken in infants at three centres in India was found to be safe and had modest efficacy of 53.6 per cent against severe rotavirus gastroenteritis.

However, the efficacy during the first year of life was higher at 56.4 per cent. The results were published in *The Lancet* journal on Wednesday.

At about 75,000 to 1,22,000 deaths per year, India accounts for about a quarter of the total number of rotavirus deaths worldwide. Rotavirus diarrhoea accounts for almost 10 per cent of all under-5 deaths and it is responsible for about 39 per cent of diarrhoea-related admissions. About 70 per cent of admissions take place in the first year of life.

The Hyderabad-based Bharat Biotech International, which had undertaken the clinical development of the vaccine and would manufacture the vaccine, has committed to make the vaccine available at not more than $1 per dose for government procurement.

The trial took place between March 2011 and November 5, 2012 in Delhi (urban), Pune in Maharashtra (rural) and Vellore in Tamil Nadu (rural and urban). The institutions involved in the study were Society for Applied Studies, Delhi; KEM Hospital Research Centre, Pune; and Christian Medical College (CMC), Vellore. Three doses of the oral vaccine were given at ages 6-7 weeks, 10 weeks and 14 weeks respectively. Other childhood vaccines were given concurrently.

Over 4,500 infants received the oral vaccine, while over 2,250 received a placebo. But for the primary per-protocol efficacy analysis, only over 4,350 vaccinated infants and nearly 2,200 infants who received a placebo were included. At the time of analysis, the median age of the infants was 17.2 months. At 96 per cent, the compliance to dosing was quite high. The follow-up of infants would continue till all infants reach the age of two years, the paper states.

Though 25 deaths were reported in the vaccine arm and 17 in the placebo arm, the deaths were not related to the vaccine, the paper notes. Nita Bhandari, from the Centre for Health Research and Development, Society for Applied Sciences, New Delhi is the lead author of the paper.

“Our findings provide good evidence of the efficacy of the 116E rotavirus vaccine and the study satisfied the primary efficacy hypothesis. 116E protected against rotavirus gastroenteritis of varying severity, with protection generally

increasing with clinical severity," the paper states. "Importantly, 116E also reduced severe gastroenteritis of any cause, showing the importance of rotavirus as a cause of severe gastroenteritis in infants in India. Findings from intention-to-treat analyses strongly supported those of the per-protocol analyses."

The rotavirus strain found in the 116E vaccine is an unusual strain in that it "rarely causes clinical disease in India and elsewhere" the paper notes.

According to the paper, the strain was found to provide protection against most of the commonly circulating rotavirus genotypes in India and in other parts of the world. The strain was identified by Prof. Maharaj K Bhan way back in the mid 1980s. He was then a paediatrician at AIIMS. He is currently with the Ministry of Science and Technology.

The vaccine uses a live, attenuated virus strain and would be given orally. The acidic environment in the stomach greatly affects the efficacy of any live virus given orally. "Infants are given an antacid prior to the vaccine administration to buffer the stomach acid," explained Dr. Krishna Ella, Chairman and Managing Director of Bharat Biotech International. "The buffering allows the virus to survive in the stomach for about 20-30 minutes." The trypsin enzyme then activates the rotavirus and helps the virus to multiply faster. The replication is faster as the virus is live.

"The strain can provide cross-protection as the outer structural proteins are similar to other rotavirus serotypes," said Dr. Ella. "It is a human neo-natal strain and very different from other rotavirus vaccines that are bovine based." It took as many as three years to identify the dosage as the strain is unique. Unlike other vaccine that have 30-40 per cent efficacy in the developing countries, the 116E vaccine has over 56 per cent efficacy.

"It is very close to getting licensed in India," Dr. Ella said. "We have developed a dedicated manufacturing facility for rotavirus vaccine. It will be ready in 4-6 months." The facility has the capacity to manufacture about 4,00,000 million doses. "India alone may require 75,000 million to 1,00,000 million doses as three doses need to be given to an infant and the birth cohort is 26 million babies a year," he noted.

The vaccine was developed by the "combined expertise and interests" of investigators from 13 institutions. Besides Bharat Biotech, DBT, Melinda Gates Foundation, other institutions in India and abroad were involved. Funding was jointly provided by the pharma company, DBT and the Foundation. PATH provided technical guidance and support.

Keywords: 116E rotavirus vaccine, rotavirus diarrhoea, Bharat Biotech, diarrhoea vaccine, infant diarrhoea, diarrhoea deaths

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