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Active surveillance for intussusception in a phase III efficacy trial of an oral monovalent rotavirus vaccine in India

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ABSTRACT

Background: Post licensure studies have identified an increased risk of intussusception following vaccination with currently licensed rotavirus vaccines, raising safety concerns generic to all rotavirus vaccines. We describe the surveillance for intussusception in a phase III clinical trial with an oral monovalent rotavirus vaccine developed from the neonatal 116E strain.
Methods: Using broad screening criteria and active surveillance, the incidence of intussusception between 6 weeks and 2 years of age was measured in 4532 children who received three doses of vaccine and 2267 children who received a placebo in the clinical trial. Possible intussusceptions were evaluated with a screening ultrasonogram. An independent intussusception case adjudication committee reviewed all intussusceptions and graded them on Brighton Collaboration criteria for diagnostic certainty.
Results: We identified twenty-three intussusceptions on ultrasound from 1361 evaluated sentinel events. Eleven were of level 1 diagnostic certainty as determined by the independent intussusception case adjudication committee. None required surgical intervention, and the earliest identified intussusception was at 36 days following the third dose in a placebo recipient. Among vaccine recipients the first event of intussusception occurred 112 days after the third dose. The incidence of ultrasound-diagnosed intussusception was 200/100,000 child-years (95% CI, 120, 320) among those receiving the vaccine and 141/100,000 child-years (95% CI, 50, 310) among those receiving the placebo. The incidence rate of confirmed intussusception among vaccine recipients was 94/100,000 child-years (95% CI, 41, 185) and 71/100,000 child-years (95% CI, 15, 206) among those receiving the placebo.
Conclusion: In this licensure study, 23 cases of intussusception were identified through an active surveillance system, but there was no temporal association with rotavirus vaccination. The use of active surveillance with broad criteria intended for ensuring safety of children participating in a trial, identified several transient intussusceptions that were of doubtful clinical significance.

1. Introduction

While rapid strides have been made in child survival globally, the Millennium Development Goal of reducing child mortality by two thirds is unlikely to be achieved in developing countries where acute gastroenteritis and respiratory illnesses constitute the bulk of post neonatal under-five mortality [1]. The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea recommends the introduction of rotavirus vaccines in National Immunization Programs (NIP) along with scaling up other proven interventions to accelerate progress in child survival [2].

A liquid oral monovalent rotavirus vaccine (Rotavac), developed from the neonatal 116E rotavirus strain, a naturally occurring

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reassortant strain G9P [11], with one bovine gene, P[11], and 10 human rotavirus genes through an innovative partnership, is projected to cost about one USD per dose and offers the prospect of an affordable rotavirus vaccine for the developing world.

Since 1999 when a tetravalent rhesus reassortant rotavirus vaccine (Rotashield, Wyeth Laboratories) was withdrawn by its manufacturer on identification of excess risk of intussusception following immunization [3,4], the safety of newer rotavirus vaccines has received intense scrutiny in large licensure and post marketing studies. Currently licensed live rotavirus vaccines, Rotarix (GlaxoSmithKline Biologicals) and Rotateq (Merck), when evaluated in large phase III studies did not reveal any excess risk of intussusception [5,6]. However post-licensure studies with both these vaccines have identified a smaller safety signal with 1–5 excess cases of intussusceptions in 100,000 immunized infants in different parts of the world [4,7–10] leading to the need to evaluate the risk of intussusception with other live rotavirus vaccines.

Given the magnitude of risk seen with Rotarix and Rotateq, prelicensure evaluation of a similar risk would require a trial size of several hundred thousand infants, making development of affordable vaccines difficult. Hence, small risks are best evaluated in post marketing surveillance through adverse event reporting systems post licensure, as recommended by national regulatory authorities and the World Health Organization [11–13]. Nonetheless, in pre-licensure trials, it is critical to remain vigilant to the risk of intussusception in trial participants and to determine if there are safety signals of larger magnitude than currently expected that might preclude licensure.

We describe the surveillance for intussusception among children enrolled in a phase III clinical trial for safety and efficacy and present some of the lessons learnt that might be relevant as countries plan post marketing surveillance for intussusception prior to or following introduction of vaccines in their NIP.

2. Methods

2.1. Subject recruitment and follow-up

Participants were enrolled, after written informed consent was obtained, in a phase III, double-blind placebo-controlled, randomized clinical trial to evaluate the efficacy of three doses of Rotavac against severe rotavirus gastroenteritis which was conducted at three sites (Delhi, Pune and Vellore) in India between 2010 and 2013. The ethics review committees of participating sites approved the protocol.

Subjects recruited between 6 and 7 weeks of age were randomized in a 2:1 ratio to receive 3 doses of vaccine or a placebo. Routine childhood vaccines were co-administered and breastfeeding was not restricted. The first one third of the participants enrolled in the study at all three sites were included in a detailed safety follow which involved study staff making daily contact for fourteen days after each dose of vaccine to solicit information on occurrence of solicited adverse events.

All children recruited in the trial were also followed up weekly until the age of 2 years for safety and efficacy endpoints. Primary caregivers were provided a mobile phone and access to the study team round the clock and were advised to contact the study team whenever the child had an episode of gastroenteritis, signs and symptoms of intussusception or any illness that required hospital referral.

2.2. Screening and management of suspected intussusception

The study used broad screening criteria for suspected intussusception to ensure all intussusceptions were identified early and treated appropriately. All children who had three or more episodes of vomiting in an hour or blood in stool or complaints of abdominal distension with an increase in abdominal girth of 2 cm or more in a 4 h period or an abdominal mass palpable per abdomen were considered to have a suspected intussusception event.

Every subject with suspected intussusception was examined by the study team and taken for pediatric consultation and hospitalized, if required. Ultrasonography was performed within eight hours and a pediatric surgeon consulted if advised by the pediatrician. Pediatric surgeons assessed children with evidence of intussusception on ultrasonography and instituted appropriate management as per treating facility protocol. All children who presented with blood in stool along with one other finding suggestive of intussusception had stool samples tested for rotavirus shedding at a central laboratory.

2.3. Adjudication of cases

An independent intussusception case adjudication committee, blinded to subject allocation reviewed clinical reports and radiologic evidence of intussusception and adjudicated on all intussusceptions based on the Brighton Collaboration Intussusception Working Group criteria for diagnostic certainty [14]. This committee was led by a senior pediatric surgeon and had a pediatric radiologist and a pediatrician as members. Brighton level 1 criteria require the presence of surgical and/or radiologic evidence of intussusception or the demonstration of intra abdominal mass by abdominal ultrasound with specific characteristics, which is proven to be reduced by hydrostatic enema on post reduction ultrasound.

2.4. Statistical methods

All children who received at least one dose of vaccine/placebo were included in the analysis. Incidence rate of intussusception along with a 95% CI was calculated assuming a Poisson distribution of events. The relative risk was also assessed for the 7-day, 14-day, and 60-day periods after any dose and for the 365-day period after the first dose.

Sensitivity and specificity of screening criteria was calculated assuming all those who did not have intussusception of any diagnostic certainty as negative for intussusception and those meeting level 1 diagnostic certainty as positive for intussusception. The sample size of the clinical trial was driven by efficacy considerations.

3. Results

The phase III clinical trial enrolled 6799 children across three sites (Delhi-3799, Pune-1500, Vellore-1500), 4532 children received vaccine and 2267 placebo. A total of 4419 (97.5%) children in the vaccine arm and 2191 (96.6%) in the placebo arm remained in the study till the age of two years contributing 8506 child-years of observation in the vaccine arm and 4248 child-years in the placebo arm. We noted a high level of compliance to study procedures with 96.3% of the subjects receiving all three doses. The analysis included all children who received at least one dose of vaccine.

During the study, 1432 events of suspected intussusception were reported in 1063 children. Of these, 46 events in 29 children in the vaccine arm and 25 events in 18 children in the placebo arm were based on caregiver's complaints of abdominal distension in the child and were unaccompanied by objective confirmation of distension or any other sign and symptom of intussusception. Although the study team followed up the cases, no ultrasound examination was considered necessary and medical intervention was not required. A total of 1361 events, 914 in the vaccine group