CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Vaccines are not one size fits all, just like medications: rotavirus vaccine study

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The current global coronavirus disease 2019 pandemic has shown us once again how important vaccination is in controlling and preventing the spread of deadly diseases. Vaccinations are one of the most tried and tested public health measures aimed at the prevention and eventual eradication of various diseases. Many debilitating diseases like polio have been eradicated in countries like India due to effective vaccination strategies. Just like with any other public health initiative, there do exist various challenges for vaccination. Efficacy and correlate of protection studies are crucial in determining which vaccine works best. The rotavirus vaccine (ROTAVAC; Bharat Biotech International Ltd., Hyderabad, India) is one such example where efficacy seen in one geographical and ethnic population is not replicated elsewhere. This has prompted various researchers and pharmaceutical companies to think about customizing vaccines to the individual needs of a particular geographic and ethnic group. In this brief communication, we look at the rotavirus vaccination story and see how it laid down the idea for customized vaccination development and what the future of vaccine development looks like.

Keywords: Rotavirus, Vaccines, ROTAVAC, Diarrhea

Globally diarrheal diseases account for around 1.3 million deaths in children under the age of 5 which is the second most common cause of death after pneumonia [1]. Management of infectious diseases requires planning at different levels such as a better understanding of the disease, prevention strategies, and treatment [2]. One of the chief goals of a country's health policy is to decrease disease burden and health care costs, in case of infectious disease like diarrhea the best strategy is timely vaccination [3].

We know from decades of research that there is no one size fits all approach to treating a disease. With varying genetic and ethnic diversity, researchers have found that the best way to treat a condition with pharmacotherapy would be to gain more pharmacogenetic information and adapt a personalized prescribing approach [4]. For effective pharmacotherapy prescribing we have tools such as PharmGKB which can help guide the prescriber to make effective prescribing decisions [5]. Now the question is if this is the very same strategy we need to adopt for vaccinations? The field of pharmacogenomics and pharmacogenetics have expanded their reach into personalized vaccination. Genetic sequencing and bioinformatics tools have helped give birth to a new field called vaccinomics [6]. Just like drug development is a long and challenging process so is vaccine development with its share of challenges. In spite of our growing knowledge of the immune system, there still remain some lacunae In our understand-

ing of some immune responses required for protection [7]. A major hurdle in the field of vaccinology is the development of products that are able to induce protective immunity in the early life period. There are clear differences between adult and neonatal immune responses in both mice and humans with respect to both humoral and cell-mediated immunity [8].

When we come to the rotavirus vaccine story, we find that there seems to be a divergence from the normal in the immune response seen in children, who get the disease and develop protective antibodies naturally based on the country and genetic background they come from [9]. One of the path-breaking researches which were done by Prof. Dr. Gangandeep Kang from the Christian Medical College, Vellore was the first of it is a kind of study in India that shed some light on how children in different regions when exposed to different levels of viral load respond to the pathogen and also how this immune response should drive our vaccination strategy. Rotavirus vaccines could have their greatest health benefit in the poorest developing countries in Africa and Asia where >85% of the estimated 527,000 deaths from rotavirus diarrhea currently occur [10]. But prior research and field studies in the case of poliovirus have taught us that children in Asia and in particular in India needed larger doses of polio vaccine in comparison to their western counterparts [11]. This was partly due to the difference in the gut physiology of these children and also the formulation type (live oral vaccination) [12]. Live oral vaccinations have their fair bit of challenges in that they have to cross several biological barriers in order to generate an immune response. In the study conducted by Prof. Kang, after institutional ethical committee approval, three contagious slums in Vellore, India, with a total population of approximately 35,000 were chosen. A cohort of 452 newborns was recruited at birth; they were followed for 3 years after birth, with home visits twice weekly. Stool samples were collected every 2 weeks, as well as on alternate days during diarrheal episodes, and were tested by means of enzyme-linked immunosorbent assay and polymerase-chain-reaction assay. Serum samples were obtained every 6 months and evaluated for seroconversion, defined as an increase in the immunoglobulin G antibody level by a factor of 4 or in the immunoglobulin A antibody level by a factor of 3 [9]. The findings of Prof. Kang's research help us understand that repeated infection induced an immune response that showed protection against moderate to severe diarrhea (82%–86%) but failed to show similar efficacy to infections of unknown status. Up until this research was done it was widely believed that repeated natural rotavirus infection would cause protection against future infections but results from Prof. Kang's study show that although there exists a corelative of protection but still not as much was seen in similar studies done in Mexico and Guinea-Bissau [13]. Another important difference between the clinical characteristics seen in this study is the onset of early childhood infections compared to a late-onset infection in the Mexico and Guinea-Bissau study. Why is this observation critical? Because for developing vaccination strategies, understanding the physiology of immune system maturity and the right time for vaccine delivery to target the high-risk period of the disease is of utmost importance. Initial belief that protection from infection is initially from homotypic and then moves to heterotypic was not seen in this study. The rates of future homotypic infections had no sign of reduction based on initial exposure to homotypic infection. Therefore, in order to address, this issue an indigenous Indian rotavirus vaccine, ROTAVAC (Bharat Biotech International Ltd., Hyderabad, India), was developed by isolating a human reassortant strain (G9P[11]) from an Indian child (Fig. 1) [14].

Phase III randomized, double blinded, placebo controlled multi-center clinical efficacy study was conducted in three sites in India in 6,800 infants (randomized 2:1 for vaccine to placebo) and demonstrated that the vaccine is safe and significantly efficacious in infants, with a vaccine efficacy of 53.6% against severe rotavirus gastroenteritis in the first year of life, and 48.9% in the second year [15,16]. This first of its kind indigenously production of a vaccine was a result of the work done by Prof. Kang which showed that rate of protec-

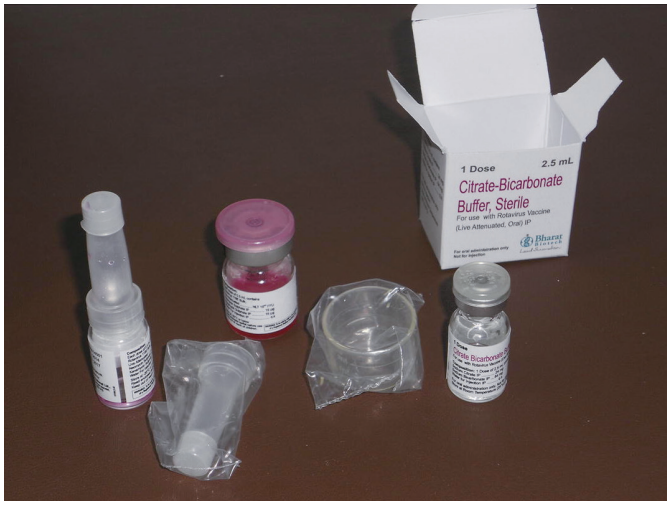

Fig. 1. ROTAVAC (Bharat Biotech International Ltd., Hyderabad, India). From Kirkwood et al. Vaccine 2019;37:7328-35 [14].

tion against diarrhea of any severity from reinfection is lower than as reported in Indian children in comparison to previous studies which looked at different populations. Therefore, just like the development of ROTAVAC (Bharat Biotech International Ltd.) took place to address this challenge so also future vaccination strategies in a similar setting need to be modified by either making changes to the number of doses or time of vaccination (neonatal or maternal). The rotavirus vaccine study, therefore, is truly a paradigm-shifting investigation that has informed us that there needs to be customized vaccination strategies for different geographical settings and also taking into account the genetic variability.

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