Indian Academy of Pediatrics (IAP)

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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children

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BASED ON ARTICLE

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ABSTRACT

Background: Lack of effective vaccination against typhoid fever leads to significant disease morbidity and mortality. With the availability of WHO pre-qualified Vi conjugate typhoid vaccines it is now possible to reduce the typhoid disease burden world over. One such Vi conjugate vaccine is Vi polysachharide conjugated to Tetanus Toxoid Vi-TT (Typbar-TCVR manufactured by Bharat Biotech India Ltd, BBLI India). Several field efficacy studies using this vaccine have been recently published. The above-mentioned study done in Malawi is unique in many ways. Malawi is a developing country with health indicators that are similar to many other developing countries making it a representative of these countries. Vi-TT or the vaccine placebo Meningococcal Conjugate A vaccine (MenA) was given simultaneously with MR vaccine at 9-11 months of age. The subjects enrolled could be HIV infected or HIV exposed. Lastly 3 year long term data on efficacy of Vi-TT is recently available and 4 years follow up data is likely to be available soon.

Methods: This study was single-center, phase 3, double-blind, individually randomized, active (placebo vaccine) controlled trial conducted in two urban townships of Malawi. This study was conducted in 9 mo to 12 years old children. The subjects were block randomized 1:1 to receive either Vi-TT or MenA vaccine. MR vaccine was given simultaneously for 9-11 mo old subjects as per the local vaccination schedule. Subjects were observed for 30 minutes for immediate side effects. Parents were instructed to take their child to one of the 4 primary health centers where there was increased passive surveillance for side effects following vaccination. If a child developed fever of > 380C of > 72 hours duration, blood culture and other routine tests including rapid malaria test were performed. Case was defined as typhoid fever if blood culture was positive. Primary endpoint of the study was efficacy of Vi-TT against blood culture proven typhoid fever and secondary endpoint was side effects. Subjects were followed up for 18-24 months.

Results: Between February 2018 to September 2018, 28,212 children received Vi-TT (14,069) or MenA (14.061). Median age of participants was 6 years. 7776 children presented with fever and 7314 (94.1%) underwent blood culture testing. 75 blood cultures in 74 subjects were positive for S. typhi, all

MDR strains. 12 of these typhoid cases were in Vi-TT group (incidence of 46.9/105) and 62 in MenA group (incidence 243.2/105). 1 child died of typhoid fever and was in MenA group. Vaccine efficacy of Vi-TT was 80.7% (95% CI 64.2-89.6). Vaccine efficacy was well sustained at 84.6% (95% CI 50-94.4) at 12 months, 82.9% (95% CI 58.1 to 92.5) at 18 months, and 78.7% (95% CI 52.8 to 91.7) at 24 months of follow up. The absolute risk reduction was 3.6 cases per 1000 vaccinated subjects and number needed to vaccinate (NNV) was 277.8. Efficacy was similar amongst boys and girls or from site to site. There was no safety concern with either of the vaccines.

Conclusions: Vi-TT from BBLI was highly effective and safe in children 9 mo-12 years old. The vaccine efficacy was sustained throughout the 2 years period of follow up.

Commentary: Annually, Typhoid fever leads to 9-14 million cases and 1.1 to 1.36 lakh deaths world over.1 The disease burden is maximum in developing countries of Asia and Africa. Poor sanitation is the necessary distant cause of typhoid fever. Most isolates of S. typhi show resistance to commonly used antibiotics (MDR), including quinolones. To make it worse, there is a huge outbreak of extended drug resistant (XRD) S. typhi resistant to even ceftriaxone in Pakistan and some other countries2. Pace of improvement in interventions like safe water, sanitation and hand hygiene is painfully slow. Hence, inclusion of effective typhoid vaccine remains the only solution. Previous typhoid vaccines have their own limitations. Vi polysaccharide vaccine has poor efficacy of 55-70% and that too short lasting for 2-3 years. They are not effective for below 2 years of age group which also has significant typhoid disease burden. Oral Ty21a vaccine had again limited efficacy and could not be given below 5 years of age as was available in capsule form.

This study shows high efficacy of above 80% of Vi-TT manufactured by BBLI, India in a developing country like Malawi where the disease incidence in 9 mo-12 years old children in the control arm was high at 245/105. The efficacy was maintained throughout the 2 years of follow up. Recently data on 3 years follow up shows that the efficacy is maintained at 80.4% and 4 years follow up data is expected soon.

There are several published data on Vi-TT vaccine from BBLI that have shown similar results.

Human volunteer challenge study done in 112 volunteers in UK showed that in post-hoc analysis the efficacy of this vaccine was 87.1% (95% CI 47.2 to 96.9) against clinical typhoid disease.[3]

A retrospective reanalysis of the immune response of the subjects enrolled in the pivotal phase III study in India showed that the sero-efficacy of this vaccine was 85% (95% CI 80-88).[4]

There are 3 more field efficacy trials done using this vaccine namely in Nepal, Bangladesh and Pakistan done under the Typhoid Vaccine Acceleration Consortium (TyVAC) project.

Nepal study was an observer blind vaccine placebo-controlled trial in 9 mo-16 years old subjects. At the end of 1 year the vaccine efficacy against blood culture positive typhoid fever was 81.6% (95% CI 58.8-91.8) and at the end of 2 years it was 79·0% (95% CI 61·9–88·5).[5,6]

Bangladesh study was a cluster randomized observer masked vaccine placebo-controlled trial done in

9 mo-16 years old subjects. Results showed that the vaccine efficacy against blood culture positive typhoid fever was 85% (97.5% CI 76-91) at 17 months follow up. 24 months follow up showed that the vaccine efficacy was sustained at 83%. 5 years follow up data will be available by end of this year. Data from the same study also looked at effectiveness of WASH (Water, Sanitation & Hand hygiene) and Vi-TT vaccine. The results showed that Vi-TT plus better WASH had adjusted effectiveness of 71% (95% CI 59-80) in Vi-TT cluster arm compared to placebo vaccine (JE vaccine) and no better WASH program.[7,8]

Lastly Pakistan study was done during the XDR typhoid outbreak when nearly 57% of S. typhi isolates were XDR. It was a cohort analysis on 6 mo-12 years old children where 13,436 vaccinated children were compared to 9971 unvaccinated children. The vaccine efficacy against overall blood culture positive typhoid cases was 94.9% (95% CI 93.2-96.3) and against culture proven XDR typhoid cases was 96.7% (95% CI 94·7–98·0).[9]

Zimbabwe faced a massive typhoid outbreak in 2017-18. GAVI funded mass vaccination in early 2019 using Vi-TT from BBLI targeting 6 mo-15 years old children (N=350,000). 3 months after the vaccination there was a sharp decrease in typhoid cases in children but not in adults (adults were not vaccinated). Blood culture positivity post-vaccination drive for S. typhi fell from 23% to 0% in children but increased from 15% to 30% in adults suggesting that you need to also immunize adults to reduce disease burden.[10]

NTAGI, India is thinking of including conjugate typhoid vaccine at 9 mo (at the time of MR vaccine) in the NIP, India. This is a very positive step and will surely help reduce typhoid disease burden in children in India as India as a top contributor of typhoid cases in the world.

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