Indian Academy of Pediatrics (IAP)

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

Lead Author
SG Kasi

UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

Upendra Kinjawadekar
IAP President 2023

GV Basavaraja
IAP President 2024

Remesh Kumar R
IAP President 2022

Vineet Saxena
IAP HSG 2022-23

Dear fellow IAPans,

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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!

Upendra Kinjawadekar
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Nitin K Shah

Tanu Singhal

Rhishikesh Thakre

Prakash Vaidya

SK Yachha

The New Zoster Vaccine

SG Kasi

Advisor, IAP ACVIP and Senior Consultant Pediatrician, Bengaluru, India.

BASED ON ARTICLE

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults
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ABSTRACT

Background: A vaccine containing the varicella–zoster virus glycoprotein E adjuvanted with AS01B (HZ/su), was studied in a phase 3 randomized, placebo-controlled study called ZOE-50, conducted in 18 countries in Europe, North America, Latin America, and Asia– Australia. Earlier, in a phase 1-2 trial in older adults, the vaccine demonstrated an acceptable safety profile and a robust immune response.

The vaccine contained 50 µg of recombinant VZV glycoprotein E and AS01B adjuvant system, which contained 50 µg of 3-O-desacyl-4′-monophosphoryl lipid A (MPL) and 50 µg of Quillaja saponaria Molina, fraction 21 (Qs21).

Methods: Of the 16,160 participants enrolled, 15,411 participants constituted the total vaccinated cohort and 14,759 (95.8%) constituted the modified vaccinated cohort. Vaccine (0.5ml) or placebo (0.9% saline solution, 0.5 ml) was administered intramuscularly into the deltoid muscle at months 0 and 2.

Follow-up commenced 1 month after the administration of the second dose. Monthly contacts and annual visits, was continued for the entire study period. This report pertains to the first 30 months of follow-up.

The primary objective of the study was to assess the overall vaccine efficacy in reducing the risk of herpes zoster, as compared with placebo, in adults who were 50 years of age or older. Secondary objectives were estimation of the vaccine efficacy in reducing the incidence of herpes zoster in the age groups 50 to 59 years, 60 to 69 years, and ≥70 years) and assessment of the safety and reactogenicity profiles of the vaccine.

Results and Outcomes: After a mean follow-up of 3.2 years, overall vaccine efficacy of 97.2% (95% CI, 93.7 to 99.0; P<0.001), was observed among participants who were 50 years of age or older. The sub-group vaccine efficacy was 96.6% (89.6-99.3) in the 50-59 years age group, 97.4% (90.1-99.7) in the 60-69 years age group and 97.9% (87.9-100) in subjects > 70 years.

Solicited and non-solicited reports of local and systemic reactions within 7 days after vaccination were noticed in 84.4% of participants in the vaccine group and 37.8% in the placebo group. Grade 3 reaction were seen in 17.0% of vaccine recipients and 3.2% of placebo recipients, which was seen more frequently after the second dose. Serious adverse effects, potential immune-mediated diseases and death were similar in the vaccine and placebo groups.

Conclusions: The risk of HZ was significantly reduced by the HZ/su vaccine, in subjects > 50 years of age. Vaccine efficacy was similar in the age groups 50-59 years, 60-69 years and > 70 years. Reactogenicity profile indicated that the vaccine was more reactogenic than the placebo**.**

Comments: Herpes zoster (HZ) results from the reactivation of latent varicella– zoster virus (VZV) and presents clinically as a unilateral vesicular skin rash in a dermatomal distribution which may be painful, or pruritic, or both.

The overall incidence of herpes zoster is 2.0 to 4.6 cases per 1000 person-years but increases with age to 10.0 to 12.8 per 1000 person-years among persons 80 years of age or older. It is estimated that approximately 1 in 3 people will develop HZ during their lifetime. Herpes zoster can occur at any age but is generally less severe in children and young adults, with the greatest morbidity and mortality seen in older adults and in immunocompromised patients. While rarely lethal with a mortality rate of (0.28–0.69 cases per 1 million), HZ causes significant morbidity and societal costs.

HZ may be complicated by secondary infections, neurological involvement such as post- herpetic neuralgia (PHN), facial paralysis, stroke, and ophthalmological adverse events such as keratitis and loss of vision.

The most common complication of herpes zoster, postherpetic neuralgia, which is also the most common infection-induced neuropathic pain, manifests as chronic neuropathic pain that can greatly limit daily activities and may result in reduced quality of life, physical functioning, and psychological well-being. The persistent pain associated with PHN is often refractory to treatment.

There is no population based data from India on the incidence of HZ in the general population. A systematic literature search review was conducted, of reports published between January 2011 and May 2020, which reported 3124 HZ clinical cases. The diagnosis of HZ was based on clinical features and Tzanck smear tests.

The mean age ranged between 29.6 and 57.3 years with 15.0% to 81.3% of cases in those > 50 years and 5.0% to 62.5% in those > 60 years.

The most frequent dermatome involved was the thoracic (38.9%–71.0%), followed by the cranial (3.3%–28.3%),cervical (4.0%–23.8%),and lumbar (5.5%–35.0%). The commonest complications observed were Post- herpetic neuralgia in 10.2– 54.7% and secondary bacterial infections in 3.5–21.0%.

The first HZ vaccines licensed for use was Zostavax of MSD.

Zostavax, a live attenuated HZ vaccine, containing ≥19 400 PFU of the OKA-Merck strain in 0.65 ml per dose, was licensed for adult > 60 years in 2006 and for adults 50-59 years in 2011. The overall efficacy against incidence of HZ was 51.3% and against PHN was 66.5%. In the ZOSTAVAX Efficacy and Safety Trial (ZEST) done in subjects 50 to 59 years of age, the observed VE was 69.8% (54.1-80.6).

In the Shingles Prevention Study (SPS) in subjects > 60 years of age, the observed overall VE was 51% (44%-58%) . The VE in the 60-69 years group was 64% (56%, 71%), 70-79 years group was 41% (28%, 52%) and in those >80 years VE was 18% (-29%, 48%). The overall VE against PHN was 39% (7%, 59%).

There was a significant decline in VE against HZ within 3-5 years of the initial vaccination. Being a live vaccine, it cannot be used in the immunocompromised. Thus Zostavax was associated with moderate protection, reduced protection in the elderly and a significantly rapid decline in efficacy, with time. On the other hand, Shingrix being an inactivated vaccine, can safely be used in the immunocompromised.

In the ZOE-50 study, done in adults > 50 years, overall vaccine efficacy of 97.2% (95% CI, 93.7 to 99.0; P<0.001), was observed among participants who were 50 years of age or older, with similar VE in age groups 50-59 years, 60-69 years and > 70 years.

In the ZOE-70 study, done in adults > 70 years, the overall vaccine efficacy observed was 89.8% (84.2-93.7). VE in 70-79 years was 90.0% (83.5-94.4) and 89.1% (74.6-96.2) in those > 70 years. The year 1 VE was 97% (88.8-99.7) with a sustained VE of 85.1% (64.4-94.9) at the end of 4 years.

The VE against PHN was 88.8% (68.7-97.1) in adults > 70 years and 91.2% (75.9-97.7) in those > 50 years. In the long term follow up (LTFU) study, with a mean follow up of 5.1 to 7.1 years, an overall VE of 84.0% (75.9–89.8) from the start of the follow-up study and 90.9% (88.2–93.2) from vaccination in ZOE-50/70. The VE from 1 month post-dose 2 to the end of year 1 was 90.9% (88.2-93.2) and 84.1% (64.4-94.0) at year 8 and the annual VE estimates were >84% for each year since vaccination and remained stable through this interim analysis period. Immune responses were also maintained at high levels throughout the study period and no safety concerns were observed.

Among adults who had undergone autologous HSCT, a 2-dose course of recombinant zoster vaccine compared with placebo showed an incidence rate ratio (IRR) of 0.32 (95% CI, 0.22-0.44; P < .001), equivalent to 68.2% vaccine efficacy. There was significant reductions in incidence of postherpetic neuralgia (vaccine, n=1; placebo, n=9; IRR, 0.1; 95% CI, 0.00-0.78; P = .02).

The overall VE against HZ after 1 dose was 56·9% (50·0–58·8) and 70.1% (68.6–71.5)

after 2 doses. In the immunocompromised the vaccine effectiveness against herpes zoster , after 2 doses was 64·1% (57·2–69·8). Vaccine effectiveness against herpes zoster ophthalmicus was 66·7%, (60·7–72·0) and postherpetic neuralgia 76·0%, (68·4–81·8) in adults.

In a claims based study, the vaccine effectiveness against HZ was 85.5% (95% CI, 83.5–87.3%) overall, with an effectiveness of 86.8% (84.6–88.7%) in individuals 50 to 79 years old and 80.3% (95% CI, 75.1–84.3%) in individuals aged >80 years. In patients with a history of live zoster vaccine within 5

years of study inclusion, vaccine effectiveness was 84.8% (75.3–90.7%).

In October 2017, the Advisory Committee on Immunization Practices (ACIP) made the following recommendations:

1. Recombinant zoster vaccine(RZV) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years, irrespective of prior receipt of varicella vaccine or ZVL.
2. RZV is preferred over ZVL for the prevention of herpes zoster and related complications.
3. Following the first dose of RZV, the second dose should be given 2–6 months later. If the second dose of RZV is given less than 4 weeks after the first, the second dose should be repeated, at least 4 weeks after the early dose.
4. For those who have received ZVL, RZV may be offered at least 2 months after the ZVL dose. On October 20, 2021, ACIP recommended 2 doses of RZV for the prevention of herpes zoster and related complications in adults aged ≥19 years who are or will be immunodeficient or immunosuppressed because of disease or therapy.

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