Indian Academy of Pediatrics (IAP)

nRICH

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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Hope for a better TB vaccine

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BASED ON ARTICLE

Safety and immunogenicity of VPM1002 versus BCG in South African newborn babies: a randomised, phase 2 non-inferiority double-blind controlled trial.
Cotton MF, Madhi SA, Luabeya AK, Tameris M, Hesseling AC, Shenje J, Schoeman E, Hatherill M, Desai S, Kapse D, Brückner S, Koen A, Jose L, Moultrie A, Bhikha S, Walzl G, Gutschmidt A, Kotze LA, Allies DL, Loxton AG, Shaligram U, Abraham M, Johnstone H, Grode L, Kaufmann SHE, Kulkarni PS.
Lancet Infect Dis. 2022 Oct;22(10):1472-1483.

BACKGROUND

Background: Tuberculosis is a major public health problem worldwide. Immunisation with Mycobacterium bovis BCG vaccine is partially effective in infants, reducing the incidence of miliary and tuberculosis meningitis, but is less effective against pulmonary tuberculosis and reactivation during adulthood. This study compared safety and immunogenicity of VPM1002—a recombinant BCG vaccine developed to address this gap—with BCG in HIV exposed and HIV unexposed newborn babies.

Methods: This double-blind, randomised, active controlled phase 2 study was conducted at four health centres in South Africa. Eligible neonates were aged 12 days or younger with a birthweight of 2·5–4·2 kg, and could be HIV exposed (seropositive mothers) or unexposed (seronegative mothers). Newborn babies were excluded if they had acute or chronic illness, fever, hypothermia, sepsis, cancer, or congenital malformation, or if they received blood products or immunosuppressive therapy. Participants were excluded if their mothers (aged ≥18 years) had active tuberculosis disease, diabetes, a history of immunodeficiency except for HIV, hepatitis B or syphilis seropositivity, received blood products in the preceding 6 months, any acute infectious disease, or any suspected substance abuse. Participants were randomly assigned to VPM1002 or BCG vaccination in a 3:1 ratio, stratified by HIV status using the random number generator function in SAS, using a block size of eight participants.

The primary outcome was safety in terms of non-inferiority (margin 15%) of VPM1002 to BCG vaccine looking at the incidence of grade 3–4 adverse drug reactions or ipsilateral or generalised lymphadenopathy of 10 mm or greater in diameter. The primary outcome was assessed in all vaccinated participants (safety population) at regular follow-up visits until 12 months after vaccination. Secondary immunogenicity outcomes were interferon-γ levels and percentages of multifunctional CD4+ and CD8+ T cells among all lymphocytes across the 12 months study period. The study was registered with ClinicalTrials.gov, NCT02391415.

Results: Between June 4, 2015 and Oct 16, 2017, 416 eligible newborn babies were randomly assigned and received study vaccine. Seven (2%) of 312 participants in the VPM1002 group had a grade 3–4 vaccine-related adverse reaction or lymphadenopathy of 10 mm or greater in diameter compared with 34 (33%) of 104 participants in the BCG group (risk difference −30·45% [95% CI −39·61% to −21·28%]; p <0·0001); VPM1002 was thus non-inferior to BCG for the primary outcome. Incidence of severe injection site reactions was lower with VPM1002 than BCG: scarring occurred in 65 (21%) participants in the VPM1002 group versus 77 (74%) participants in the BCG group (p<0·0001); ulceration occurred in one (<1%) versus 15 (14%; p<0·0001); and abscess formation occurred in five (2%) versus 23 (22%; p<0·0001).

Restimulated IFNγ concentrations were lower in the VPM1002 group than the BCG group at week 6, week 12, month 6, and month 12. The percentage of multifunctional CD4+ T cells was higher in the VPM1002 group than the BCG group at day 14 but lower at week 6, week 12, month 6, and month 12. The percentage of multifunctional CD8+ T cells was lower in the VPM1002 group than the BCG group at week 6, week 12, and month 6, but did not differ at other timepoints.

Conclusions: VPM1002 was less reactogenic than BCG and was not associated with any serious safety concern. Both vaccines were immunogenic, although responses were higher with the BCG vaccine. VPM1002 is currently being studied for efficacy and safety in a multicentric phase 3 clinical trial in babies in sub-Saharan Africa.

COMMENTARY

For prevention of TB, BCG vaccine has been our only option for more than 100 years. However, we are aware that BCG vaccine has several limitations. BCG gives protection only against severe forms of childhood TB like TB meningitis and disseminated TB, but it does not protect adolescents and adults, who account for the majority of TB cases and transmission. Basically, BCG does not prevent primary infection and, does not prevent reactivation of latent pulmonary infection and as a result, has limited impact on transmission of Mtb. The WHO 'End TB' Strategy has a target of a 95% reduction in TB mortality and a 90% reduction in TB incidence, worldwide, by 2035 which cannot be achieved with BCG vaccine alone.

There is also a significantly high risk of disseminated BCG (dBCG) disease in HIV-positive infants, with rates approaching 1%. BCG vaccine is contraindicated in people with impaired immunity, and WHO does not recommend BCG vaccination for children with symptomatic HIV infection. Therefore, we need better TB vaccines that are effective and safe across all age groups, particularly adults and adolescents and immune compromised individuals too.

Many candidate TB vaccines are in the development. These candidates are at various stages of development from early pre-clinical development through to clinical trials phase 1 to phase 2b/3 trials. These candidates range from recombinant antigens to be delivered with adjuvant, antigens to be delivered by viral vectors, and genetically modified live bacterial vaccines, recombinant BCG vaccines such as VPM1002 and a live attenuated M. tuberculosis vaccine, MTBVAC.

VPM1002, a genetically modified BCG vaccine has been developed in Germany and subsequently taken over by Serum Institute of India. VPM1002 is based on the Danish strain of BCG, and expresses a listeriolysin that enables the bacilli to access the cytoplasm of the host cell, potentially enhancing CD8+ T-cell activation. In mice, VPM1002 provided superior protection against aerosol M tuberculosis infection compared to BCG and improved survival in severe combined immunodeficiency mice. The vaccine was found safe and immunogenic in two Phase 1 studies in adults and one Phase 2 study in newborns. The immune response by VPM1002 was comparable to that of BCG. These studies used the original hygromycin-resistant formulation of VPM1002.

The paper by Cotton et al compared the safety and immunogenicity of VPM1002, to BCG in a double-blind, randomized, controlled phase 2b study in newborns in South Africa. The study also included HIV exposed children. The study also bridged the hygromycin-resistant formulation to a hygromycin-sensitive formulation.

In terms of the incidence of grade 3 and 4 adverse drug reactions as well as lymphadenopathy, VPM1002 was found comparable to BCG. VPM1002 did not cause abscess formation or scarring in HIV-exposed infants, whereas BCG caused abscess or scars in 22.1% of cases and 74% of cases, respectively. Thus, VPM1002 was significantly less reactogenic than BCG. Since HIV-infected infants are at risk of developing disseminated BCG infections, this is an encouraging news.

Although it was less immunogenic than BCG six weeks after vaccination in terms of the frequency of CD4+ multifunctional T cells or secreted IFNg, vaccination with VPM1002 was immunogenic. In any case, unlike many other vaccines, direct correlation between immune response and protective efficacy has not been proven for BCG vaccine, and therefore, we cannot read too much in the immunogenicity results. More infants in the BCG group showed positive Mantoux skin tests at 12 months than in the VPM1002 group, but only a few infants developed TB (1 of 104 for BCG and 5 of 302 for VPM1002).

Apart from TB, BCG vaccine is also known to induce non-specific protection against unrelated infections in newborns through the phenomenon known as innate immune memory or trained immunity. Obviously, it is not possible to detect these effects in small trials, but VPM1002 is expected to provide such benefits. Larger post-marketing studies may answer this question.

VPM1002 is currently being tested in three large Phase 3 trials to assess clinical efficacy of the vaccine; first in household contacts of TB patients in India, second also in India in prevention of TB recurrence in patients who were cured of TB and third in African newborns as an EPI vaccine. These studies will answer the question of its protective efficacy. However, the paper by Cotton et al definitely gives a hope for a better TB vaccine.

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