No long-term evidence of hyporesponsiveness after use of pneumococcal conjugate vaccine in children previously immunized with pneumococcal polysaccharide vaccine

Paul V. Licciardi, PhD,[a,b] Zheng Quan Toh, BSc(Hons),[a] Elizabeth A. Clutterbuck, PhD,[c] Anne Balloch, MSc,[a] Rachel A. Marimla, BBiomed(Hons),[a] Leena Tikkanen, MSc,[a] Karen E. Lamb, PhD,[b,d] Kathryn J. Bright, BSN,[a] Uraia Rabuatoka, BMLSc,[e] Lisi Tikoduadua, MBBS,[f] Laura K. Boelsen, BBiomedSc(Hons),[a,b] Eileen M. Dunne, PhD,[a] Catherine Satzke, PhD,[a,b,g] Yin Bun Cheung, PhD,[h,i] Andrew J. Pollard, PhD,[c] Fiona M. Russell, PhD,[b,j] and Edward K. Mulholland, MD[a,k,l] *Melbourne, Parkville, and Darwin, Australia, Oxford and London, United Kingdom, Suva, Fiji, Singapore, and Tampere, Finland*

Background: A randomized controlled trial in Fiji examined the immunogenicity and effect on nasopharyngeal carriage after 0, 1, 2, or 3 doses of 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar) in infancy followed by 23-valent pneumococcal polysaccharide vaccine (23vPPV; Pneumovax) at 12 months of age. At 18 months of age, children given 23vPPV exhibited immune hyporesponsiveness to a micro-23vPPV (20%) challenge dose in terms of serotype-specific IgG and opsonophagocytosis, while 23vPPV had no effect on vaccine-type carriage.

Objective: This follow-up study examined the long-term effect of the 12-month 23vPPV dose by evaluating the immune response to 13-valent pneumococcal conjugate vaccine (PCV13) administration 4 to 5 years later.

Methods: Blood samples from 194 children (now 5-7 years old) were taken before and 28 days after PCV13 booster immunization. Nasopharyngeal swabs were taken before PCV13 immunization. We measured levels of serotype-specific IgG to all 13 vaccine serotypes, opsonophagocytosis for 8 vaccine serotypes, and memory B-cell responses for 18 serotypes before and after PCV13 immunization.

Results: Paired samples were obtained from 185 children. There were no significant differences in the serotype-specific IgG, opsonophagocytosis, or memory B-cell response at either time point between children who did or did not receive 23vPPV at 12 months of age. Nasopharyngeal carriage of PCV7 and 23vPPV serotypes was similar among the groups. Priming with 1, 2, or 3 PCV7 doses during infancy did not affect serotype-specific immunity or carriage.

Conclusion: Immune hyporesponsiveness induced by 23vPPV in toddlers does not appear to be sustained among preschool children in this context and does not affect the pneumococcal carriage rate in this age group. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Pneumococcal polysaccharide vaccine, 23vPPV, hyporesponsiveness, memory B cell, opsonophagocytosis, antibody*

Streptococcus pneumoniae (the pneumococcus) is a gram-positive bacterium that is responsible for a large burden of morbidity and mortality in children less than 5 years of age worldwide.[1] According to the latest World Health Organization (WHO) estimates, pneumococcal diseases, such as pneumonia, meningitis, and septicemia, cause 826,000 child deaths per year, mostly in developing countries.[2]

Protection against pneumococcal diseases is achieved principally through vaccination, with 2 types of vaccines currently licensed and implemented in many countries. Pneumococcal conjugate vaccines (PCVs), whereby the capsular polysaccharide from up to 13 serotypes is coupled to a protein carrier, have had a remarkable effect on vaccine-type disease in every setting in which they have been used.[3] At present, PCVs containing 10 or 13 common disease-causing serotypes[3] are available. In comparison, the 23-valent pneumococcal polysaccharide vaccine (23vPPV; Pneumovax; Merck & Co, Whitehouse Station, NJ) is a plain polysaccharide vaccine representing the 23 pneumococcal serotypes that are responsible for more than 90% of disease in

From [a]Pneumococcal Research, [d]the Clinical Epidemiology and Biostatistics Unit, and [j]the Centre for International Child Health, Murdoch Childrens Research Institute, Melbourne; [b]the Department of Paediatrics and [g]the Department of Microbiology and Immunology at the Peter Doherty Institute for Infection and Immunity, University of Melbourne, Parkville; [c]the Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford; [e]Mataika House, National Centre for Communicable Disease Research, Suva; [f]Colonial War Memorial Hospital, Suva; [h]the Center for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore; [i]the Department of International Health, University of Tampere; [k]Menzies School of Health Research, Darwin; and [l]the London School of Hygiene and Tropical Medicine, London.

Supported by a National Institutes of Allergy and Infectious Disease grant (1R01AI085198-01A1). P.V.L. is a recipient of an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship. Y.B.C. was supported by the National Research Foundation, Singapore, under its Clinician Scientist Award (award no. NMRC/CSA/039/2011) administered by the Singapore Ministry of Health's National Medical Research Council. E.A.C. was supported by the NIHR Oxford Biomedical Research Centre. A.J.P. is a Jenner Institute Investigator and a James Martin Senior Fellow. We also acknowledge the support of the Victorian Government's Operational Infrastructure Support Program. The views expressed in this manuscript do not necessarily reflect the views of the UK Department of Health or Joint Committee on Vaccination and Immunisation.

Disclosure of potential conflict of interest: C. Satzke receives funds from Merck, Sharp & Dohme. A. J. Pollard receives research funding from Pfizer and GlaxoSmithKline and is also chair of the UK Department of Health's Joint Committee on Vaccination and Immunisation. E. K. Mulholland serves on the advisory board for Merck & Co. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 17, 2015; revised December 16, 2015; accepted for publication December 28, 2015.

Corresponding author: Paul V. Licciardi, PhD, Pneumococcal Research, Murdoch Childrens Research Institute, Melbourne, Australia. E-mail: paul.licciardi@mcri.edu.au.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.12.1303

Abbreviations used
CPS: Cell-wall polysaccharide
FiPP: Fiji Pneumococcal Project
MOPA: Multiplexed opsonophagocytic assay
OI: Opsonization index
OPA: Opsonophagocytic assay
PBS-T: PBS containing 0.05% (vol/vol) Tween 20
PCV: Pneumococcal conjugate vaccine
PCV7: 7-Valent pneumococcal conjugate vaccine
PCV13: 13-Valent pneumococcal conjugate vaccine
23vPPV: 23-Valent pneumococcal polysaccharide vaccine
WHO: World Health Organization

the United States.[4] However, 23vPPV is not recommended for use in children less than 2 years of age because of immaturity of their immune system to respond to polysaccharide antigens.[5] Instead, 23vPPV is administered to older children after a primary series of PCV and in some settings to immunocompromised and healthy adults from the age of 65 years. In Australia indigenous children have a higher rate of pneumococcal disease. Until recently, in addition to PCV in infancy, these children also received 23vPPV as a booster vaccine at 18 months because of its broader serotype coverage.[6]

Vaccine efficacy of 23vPPV for the prevention of invasive pneumococcal disease in adults was found to be 74% in a Cochrane review[7] based on studies that mainly used older-generation vaccines but has been reported to be much lower in some studies,[8] whereas protection against pneumonia or death has been difficult to establish.[7] Early trials of 23vPPV in young children in Papua New Guinea demonstrated a 59% efficacy against acute lower respiratory infections and a significant reduction in mortality.[9] In the Fiji Pneumococcal Project (FiPP) we set out to evaluate the utility of 23vPPV as a booster vaccine in children primed with various schedules of 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar; Pfizer, New York, NY). We examined the response to a 20% challenge dose of 23vPPV at 17 months of age (to mimic infection) in children previously primed with 0 to 3 doses of PCV7 and randomized to receive or not receive a full dose of 23vPPV at 12 months. This was designed to examine the immunologic effects of 23vPPV at 12 months of age. Although children less than 12 months of age might not be expected to respond to a polysaccharide vaccine, the children given 23vPPV at 12 months of age in this study had good booster antibody responses to the PCV7 types that were higher than those in children who did not receive 23vPPV. However, these 23vPPV-vaccinated children failed to boost these responses further when given a 20% 23vPPV challenge dose at 17 months of age, whereas children who did not receive 23vPPV at 12 months of age produced higher antibody levels to all PCV7 and almost all non-PCV7 serotypes.[10] This has led to safety concerns for these children given the substantial burden of pneumococcal carriage and disease in this population.

We now report the findings of a long-term follow-up investigation of immune hyporesponsiveness in these children. We investigated whether the immune hyporesponsiveness observed at 18 months of age has had a deleterious effect on immune competence, nasopharyngeal carriage of pneumococci, and associated clinical outcomes measured in these children at 5 to 7 years of age.

METHODS

Study population and samples

The study design and details of FiPP (2003-2008) have been reported previously.[10-12] Briefly, healthy Fijian infants (n = 552) were randomized to receive a primary series of 0, 1, 2, or 3 doses of PCV7, with half the children randomized to receive 23vPPV at 12 months of age. Children given 0 or 1 PCV7 doses during the primary series were given a catch-up PCV7 dose at 2 years of age (Table I). Between March 2011 and February 2012, families who had participated in FiPP and previously agreed to be contacted for follow-up studies were invited to participate in a follow-up study. After consent, on the first visit, all children had 10 mL of blood drawn into a sodium heparin tube, and a nasopharyngeal swab was taken according to standard methods.[13] In addition, they were each administered a single dose of 13-valent pneumococcal conjugate vaccine (PCV13). A second blood sample was taken 28 days later.

This study was approved by the Fiji National Research Ethics Review Committee and the Royal Children's Hospital Human Research Ethics Committee in Melbourne, Australia.

Measurement of pneumococcal serotype-specific IgG levels by means of ELISA

Serotype-specific IgG levels to all 23 serotypes were measured by using a previously published modified WHO ELISA developed in our laboratory (see details in the Methods section in this article's Online Repository at www.jacionline.org).[14]

Opsonophagocytosis assay

All opsonophagocytic assays (OPAs) were undertaken in our laboratory based on previously published multiplexed methods (multiplexed opsonophagocytic assay [MOPA]; see details in the Methods section in this article's Online Repository).[15]

Enumeration of pneumococcus-specific memory B cells

We undertook the measurement of pneumococcus-specific memory B cells on site in Fiji using a previously established method (see details in the Methods section in this article's Online Repository).[16]

Measurement of nasopharyngeal carriage

Pneumococcal carriage was measured by using standard culture-based methods similar to the original FiPP study (see details in the Methods section in this article's Online Repository).[12,13]

Hospitalization data

The Colonial War Memorial Hospital in Suva, Fiji, uses a computerized system for recording admissions and discharges (Patient Information System). All discharges were entered into a nationwide linked database, and a search for admissions was performed by using demographic identifiers or hospital numbers. In addition to asking parents whether their child has been hospitalized at the time of the first study visit, a thorough search of the computerized discharge system based on the name and date of birth from the commencement of the study up to the present time to identify all hospital admissions involving all children in the original study (n = 552) was undertaken. Serious adverse events in children aged greater than 12 months and by receipt or not of the 12-month 23vPPV was assessed. The laboratory results of any lumbar punctures or blood cultures taken were recorded.

Statistical analysis

Serotype-specific IgG and OPA titers were presented as geometric mean concentrations or geometric mean opsonization indices with 95% CIs,