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Introduction of the 13-valent pneumococcal conjugate vaccine in an isolated pneumococcal vaccine-naïve indigenous population

To the Editor:

The introduction of pneumococcal conjugate vaccines (PCVs) has the greatest impact in populations that are most affected by pneumococcal carriage and disease, such as indigenous children [1]. Although ∼10% of the South American population consists of indigenous people living in remote settings, to our knowledge PCVs have not been evaluated in native South American children. The Warao people are an Amerindian population residing in wooden houses along the Orinoco River delta in Venezuela. Almost one-third of Warao children die during childhood and respiratory tract infections are a major cause of death [2]. This study is the first to evaluate the impact of 13-valent (PCV13) vaccination on nasopharyngeal colonisation rates and antibody response in PCV-naïve indigenous South American children.

From May to November 2012, 504 Warao children aged 6 weeks to 59 months residing in nine communities were vaccinated. Before and at a median 6.7 weeks after primary PCV13 series we obtained nasopharyngeal swabs (n=424) and serum samples (n=421). The primary series consisted of three vaccine doses for children

aged ⩽6 months and two and one dose(s) for children aged 7–23 months and 24–59 months, respectively, following Centers for Disease Control and Prevention guidelines [3]. Siblings of vaccinated children (aged 5–10 years, n=190) and caregivers (n=269) were included as unvaccinated community controls, bringing the total number of subjects sampled pre- and post-vaccination to n=883.

Pneumococcal serotype-specific immunoglobulin G antibodies were measured using a fluorescent bead-based multiplex immunoassay. Antibody concentrations were log-transformed and compared using unpaired t-tests or ANOVA and Bonferroni *post hoc* tests. Nasopharyngeal samples were cultured using standard methods and serotyped using multiplex PCR. Since serotypes of serogroups 6, 9 and 19 could not be determined using PCR, the Quellung reaction was used. Carriage rates pre- and post-vaccination were compared using the McNemar test. We used single imputation using SPSS (IBM, Armonk, NY, USA) to correct for 43 samples in which the Quellung reaction failed to determine the serotype, which suffices in cases where the number of missing values is limited, as in our study [4].

The study was approved by the ethical committee of the Instituto de Biomedicina (Caracas, Venezuela), the Delta Amacuro indigenous health office and community leaders. The study was registered in a primary World Health Organization registry (identifier number RPCEC00000158).

PCV13 appeared to be highly immunogenic in children aged 6 weeks to 6 months with geometric mean concentrations (GMCs) as much as >20 times higher than generally observed [5, 6]. Adequate antibody concentrations (*i.e.* ⩾0.35 μg·mL^{-1}) in ⩾90% of children aged 7–23 months were observed for 11 out of 13 serotypes. In children aged 24–59 months, this was observed for only five out of 13 serotypes (table 1). Antibody concentrations were two to three times higher in children aged 7–23 months and three to 10 times higher in children aged ⩽6 months compared with those aged 24–59 months. Low antibody concentrations in children aged 24–59 months may be partly explained by previous colonisation with the vaccine serotype. Of the seven serotypes carried by more than one child pre-vaccination, significantly decreased post-vaccination antibody concentrations were observed for serotypes 6A and 23F compared with noncarriers (0.35 μg·mL^{-1} *versus* 1.7 μg·mL^{-1}, p<0.01 and 0.38 μg·mL^{-1} *versus* 1.1 μg·mL^{-1}, p=0.017, respectively). However, serotype-specific hyporesponsiveness was also observed in children aged <24 months for serotypes 6A and 19A (1.5 μg·mL^{-1} *versus* 5.3 μg·mL^{-1}, p=0.01 and 1.1 μg·mL^{-1} *versus* 4.0, p=0.048, respectively), albeit with higher overall antibody concentrations.

Pneumococcal carriage varied between communities, ranging from 50% to 88% in children. In the 424 vaccinated children vaccine-type carriage decreased significantly (39–29%, p<0.01), while no significant decrease of vaccine-type carriage was detected in 459 unvaccinated controls (14–12%, p=0.60). Among vaccinated children, a statistically significant decrease in vaccine-type carriage was observed in those aged <24 months (45–28%, p<0.01), but not in children aged 24–59 months (36–29%, p=0.078).

The study area, which is heavily affected by high prevalence rates of pneumococcal carriage and disease, was extremely remote and only accessible by traversing the multiple waterways in the river delta by boat. Nevertheless, a large number of subjects were included in this study. Our results demonstrate for the first time that it may be necessary to adapt the currently recommended vaccine schedules for indigenous children living in unique geographical settings. While high antibody concentrations and a significant reduction in vaccine-type carriage 7 weeks post-vaccination were observed in young children, limited carriage reduction and lower antibody concentrations were measured in Warao children aged 24–59 months. In contrast, in nonindigenous children aged 24–72 months, ⩾90% generally reaches GMCs ⩾0.35 μg·mL^{-1} for most serotypes and vaccine-type carriage is reduced 1 month after a single PCV dose [7–9]. Lower antibody concentrations in Warao children aged ⩾24 months might be the consequence of cumulative exposure to immune-modulating helminth infections [10]. In addition, hyporesponsiveness to some colonising serotypes was observed in Warao children of all ages. However, in carriers, GMCs approximated the threshold of 0.35 μg·mL^{-1} for two serotypes only in those aged 24–59 months. This phenomenon was previously described in infants [11] and in high-risk children with chronic conditions such as asplenia or immunocompromising disease [9]. For children aged ⩾24 months considered to be at high risk, two-dose regimens are already recommended [3]. Possibly, this recommendation needs to be extended to indigenous children. The importance of adequate antibody concentrations in children ⩾24 months lies in the establishment of herd immunity [12], since there is a large pneumococcal reservoir in Warao children aged ⩾24 months [1]. However, it is difficult to define adequate antibody concentrations. Although 0.35 μg·mL^{-1} is widely used for all serotypes, serotype-specific correlates of protection appear to vary [13]. This is particularly important for serotype 6B, which was the least immunogenic serotype in our study, while it is responsible for almost 10% of the invasive pneumococcal disease cases in Latin America [14]. It has been suggested that an antibody concentration of 0.16 μg·mL^{-1} is sufficient to protect against disease by serotype 6B [13]. However, the proportion of children aged 24–59 months with concentrations for 6B ⩾0.16 μg·mL^{-1} was still low (67%). Non-antibody mediated immune responses also seem to play an important role in

TABLE 1 Pneumocccal serotype-specific antibody geometric mean concentrations (GMCs) and proportion of antibody concentrations ⩾0.35 μg·mL^{-1} following 13-valent pneumococcal conjugate vaccine (PCV13) vaccination of Warao Amerindian children aged 6 weeks to 59 months

	Children with one vaccine dose (24–59 months)			Children with two vaccine doses (7–23 months)			Children with three vaccine doses (6 weeks to 6 months)			Differences in antibody concentration 6 weeks to 23 months *versus* 24–59 months
	GMC post-vaccination (95% CI)	Fold rise post- *versus* pre-vaccination	IgG ⩾0.35 μg·mL^{-1}	GMC post-vaccination (95% CI)	Fold rise post- *versus* pre-vaccination	IgG ⩾0.35 μg·mL^{-1}	GMC post-vaccination (95% CI)	Fold rise post- *versus* pre-vaccination	IgG ⩾0.35 μg·mL^{-1}	p-value
Subjects n		287			109			25		421
Serotypes										
1	1.2 (1.1–1.4)	11	84	4.3 (3.4–5.3)	38	97	21.7 (15.9–29.6)	241	100	<0.01
3	3.7 (3.3–4.1)	13	99	7.0 (5.9–8.4)	28	100	10.4 (7.7–14.0)	54	100	<0.01
4	0.67 (0.59–0.75)	7	74	2.2 (1.8–2.6)	21	95	8.1 (5.7–11.6)	123	100	<0.01
5	1.3 (1.1–1.5)	16	87	4.1 (3.3–5.1)	60	100	25.4 (18.6–34.7)	541	97	<0.01
6A	1.6 (1.3–2.0)	34	80	3.8 (2.9–5.0)	152	91	13.6 (3.4–24.9)	205	96	<0.01
6B	0.36 (0.28–0.46)	9	51	0.37 (0.26–0.52)	19	57	3.5 (1.7–7.2)	51	88	0.037
7F	5.7 (5.1–6.4)	61	100	10.6 (9.1–12.4)	105	100	29.7 (22.8–38.6)	395	100	<0.01
9V	0.94 (0.80–1.1)	10	75	1.9 (1.5–2.4)	29	90	11.7 (8.1–16.9)	180	100	<0.01
14	2.0 (1.7–2.4)	22	86	4.3 (3.5–5.2)	97	99	19.2 (14.9–24.8)	100	100	<0.01
18C	1.8 (1.6–2.1)	25	91	4.4 (3.6–5.3)	70	100	18.2 (14.0–23.6)	239	100	<0.01
19A	1.6 (1.4–1.9)	8	90	3.2 (2.6–4.0)	16	100	9.1 (6.9–12.0)	63	100	<0.01
19F	4.9 (4.3–5.7)	20	97	9.5 (7.5–12.1)	70	98	31.9 (22.5–45.2)	96	100	<0.01
23F	1.0 (0.82–1.2)	10	70	1.1 (0.85–1.5)	19	79	9.2 (4.9–17.2)	101	96	<0.01

Data are presented as %, unless otherwise stated. Ig: immunoglobulin.

acquisition and duration of pneumococcal carriage. Recently, it was shown that the balance between T-helper 17 and regulatory T-cells is critically associated with the clearance of carriage from the nasopharynx [15]. This balance is also distorted by chronic intestinal helminth infections [10].

The findings of our study have to be interpreted in the light of its limitations. The study had no age-matched comparator arm since it was deemed unethical to deprive vulnerable Warao children of the vaccine after reaching these geographically isolated areas. Additionally, a comparison between communities would be affected by the difference in baseline colonisation rates. Because all samples were taken during the rainy season, it is very unlikely that the observed carriage shifts were season-related. The inclusion of unvaccinated siblings and caregivers clearly showed that vaccine-type carriage only decreased significantly in vaccinated children.

In conclusion, while PCV13 was highly immunogenic in Warao children aged <24 months, children aged 24–59 months did not reach adequate antibody concentrations for a majority of serotypes after one catch-up dose. Higher antibody concentrations in younger children were accompanied by a significant decrease in nasopharyngeal carriage of vaccine-type pneumococci. Before PCV guidelines based on studies in healthy non-native children are extrapolated to vulnerable indigenous childhood populations, critical evaluation of the need for possible adjustments in dosing schedules is warranted.

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PCV13 catch-up regimens for children aged ⩾24 months may need to include more than one vaccine dose http://ow.ly/lstI3023i2R

Lilly M. Verhagen[1,2,3], Ismar A. Rivera-Olivero[1], Meyke Hermsen[4], María Carolina Sisco[1], Mailis Maes[1], Berenice del Nogal[5], Debby Bogaert[3], Guy A.M. Berbers[6], Peter W.M. Hermans[2], Marien I. de Jonge[2] and Jacobus H. de Waard[1]

[1]Laboratorio de Tuberculosis, Instituto de Biomedicina, Universidad Central de Venezuela, Caracas, Venezuela. [2]Laboratory of Paediatric Infectious Diseases, Dept of Paediatrics, Radboud Institute for Molecular Life Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands. [3]Dept of Paediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital Utrecht, Utrecht, The Netherlands. [4]Dept of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands. [5]Dept of Paediatrics, Children's Hospital J.M. de los Ríos, Universidad Central de Venezuela, Caracas, Venezuela. [6]Centre for Infectious Disease Control, National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

Correspondence: Lilly M. Verhagen, Wilhelmina Children's Hospital Utrecht, Dept of Paediatric Immunology and Infectious Diseases, Lundlaan 6 3584 EA Utrecht, The Netherlands. E-mail: L.M.Verhagen-4@umcutrecht.nl

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Multidrug-resistant tuberculosis in children in northwest Russia: an observational cohort study

To the Editor:

Russia has the third highest absolute number of multidrug-resistant (MDR) tuberculosis (TB) cases in the world [1], yet little is known about the scale of childhood MDR-TB in the country; available publications are limited to small case series in older children [2, 3]. Successful treatment outcomes for children with MDR-TB vary widely in other settings, ranging from 53% to 97% [4].

The Arkhangelsk region has one of the highest rates of MDR-TB in Russia [5]. The first paediatric MDR-TB case was registered in 2001. The Arkhangelsk Regional Tuberculosis Dispensary, a state healthcare tertiary TB centre, coordinates care for all patients with drug-resistant TB in the region and works closely with two paediatric sanatoriums.

We conducted a retrospective cohort study of all children (<18 years) diagnosed with MDR-TB in the region, from January 1, 2001 to December 31, 2012 with follow-up data to December 31, 2015. Data were extracted from patient health records and treatment cards. In the Russian national TB programme, childhood TB is disaggregated into younger children (<15 years) and adolescents (15–18 years). This cut-off was preserved to align with country reporting.

MDR-TB was considered as confirmed or clinically-diagnosed. Confirmed cases were verified by culture and drug-sensitivity testing and/or molecular testing. Clinically diagnosed cases were defined according to published consensus definitions [6] and TB severity was categorised based on established criteria [7]. Children with sputum smear- or culture-positive MDR-TB were treated as in-patients at the dispensary until they were considered non-infectious; most sputum culture-negative cases were treated in the paediatric sanatoriums. A few children were managed at home with directly observed therapy (DOT).