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Infant vaccination timing: Beyond traditional coverage metrics for maximizing impact of vaccine programs, an example from southern Nepal

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ABSTRACT

Background: Immunization programs currently measure coverage by assessing the proportion of children 12–24 months who have been immunized but this does not address the important question of when the scheduled vaccines were administered. Data capturing the timing of vaccination in first 6 months, when severe disease is most likely to occur, are limited.
Objective: To estimate the time to Bacillus Calmette–Guérin (BCG) (recommended at birth), diphtheria-tetanus-pertussis-H, influenza b-hepatitis B (DTP-Hib-HepB), and oral polio vaccine (OPV) (recommended at 6, 10, and 14 weeks) vaccinations and risk factors for vaccination delay in infants <6 months of age in a district in southern Nepal where traditional coverage metrics are high.
Design/methods: Infants enrolled in a randomized controlled trial of maternal influenza vaccination were visited weekly at home from birth through age 6 months to ascertain if any vaccinations had been given in the prior week. Infant, maternal, and household characteristics were recorded. BCG, DTP-Hib-HepB, and OPV vaccination coverage at 4 and 6 months was estimated. Time to vaccination was estimated through Kaplan–Meier curves; Cox-proportional hazards models were used to examine risk factors for delay for the first vaccine.
Results: The median age of BCG, first OPV and DTP-Hib-HepB receipt was 22, 21, and 18 weeks, respectively. Almost half of infants received no BCG by age 6 months. Only 8% and 7% of infants had received three doses of OPV and DTP-Hib-HepB, respectively, by age 6 months.
Conclusion: A significant delay in receipt of infant vaccines was found in a prospective, population-based, cohort in southern Nepal despite traditional coverage metrics being high. Immunization programs should consider measuring time to receipt relative to the official schedule in order to maximize benefits for disease control and child health.

1. Introduction

Immunization is the primary means of prevention for several childhood infectious diseases. Approximately 2–3 million deaths are prevented each year due to immunization with diphtheria, tetanus, pertussis, and measles vaccines [1]. Since the introduction of the Expanded Programme on Immunization (EPI) in 1974 the percentage of children protected against six diseases (tuberculosis, diphtheria, tetanus, pertussis, polio, and measles) increased from

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5% to 83% (measured at 12–23 months of age) [2–4]. For example, the World Health Organization (WHO) estimates that since the end of the 1980s, 80% of children worldwide received pertussis vaccines, preventing approximately 38 million cases and 600,000 deaths annually [5]. Despite tremendous progress, global coverage remains below the target of 90% diphtheria-tetanus-pertussis-3 (DTP3) coverage [6]. While EPI has dramatically reduced the incidence of vaccine-preventable diseases they remain an important contributor to child deaths in low and middle-income countries [7].

Delay in vaccination is especially important for infants who are generally at high risk for severe morbidity and mortality from these diseases [8]. While infants might have partial protection from passive transfer of antibodies from their mothers, this immunity eventually wanes, requiring active immunization for infants to be protected against disease [9].

In Nepal, DTP3 vaccine coverage increased from 54% of children fully vaccinated by 12–23 months of age in 1995 to 90% in 2012; similar increases were seen for oral polio vaccine-3 (OPV3) (50–90%) and Bacillus Calmette–Guérin (BCG) (76–96%) [10]. Even though current coverage is high, this measure does not capture the timing of vaccine receipt relative to the official schedule. Recent estimates of coverage at 6 months in low and middle-income countries found DTP3 coverage was just 36% and BCG coverage was 85% [11]. A focus on vaccine receipt as close as possible to the official schedule could significantly improve the benefits of immunization programs. Unfortunately, population-based data on early vaccination coverage using active surveillance in low-income countries are lacking. This prospective, population-based cohort study aimed to estimate vaccination timing and risk factors for delay in the first 6 months of life in a rural district in southern Nepal. This information is important for policy makers to understand potential delays in vaccination and which populations are most at risk for targeted interventions to improve timeliness of uptake.

2. Methods

2.1. Settings and population

The setting of the study was in nine northern Village Development Committee areas in Sarlahi District, located in the central *terai* (low lying plains) region of Nepal and nested within a randomized controlled trial of maternal influenza vaccination during pregnancy [12]. At the start of the trial, prevalent pregnancies were identified through a census of all households in the catchment area. For the duration of the trial, field workers visited all households in the community where married women (15–40 years) resided every 5 weeks for surveillance of incident pregnancies. Once a pregnancy was identified women were asked for their consent to participate in the trial. Through the house-to-house surveillance, 4632 pregnancies were identified. Of these, 14 women were lost to follow-up before enrollment, 19 refused, 105 lost their fetus before enrollment, 799 were identified >34 weeks gestation (primarily at the beginning of the study), 1 had an egg allergy, and 1 intended to leave the study area and thus was not eligible. Between April 25, 2011 and September 9, 2013, 3693 pregnant women between 17 and 34 weeks gestation were randomized and vaccinated with either an influenza vaccine or placebo. All participants received ancillary benefits, which included a 90-day supply of iron-folic acid tablets, deworming medication (single dose of albendazole), clean birthing kit, chlorhexidine ointment for umbilical cord care, tetanus toxoid vaccine, if indicated, and health education messages, in addition to referral for antenatal services in the local health care system. At the time of the study, the vaccines recommended by the Nepal vaccination program in the first 6 months were BCG (at birth), OPV and DTP-Hib-HepB (both at 6, 10, and 14 weeks) (Table 1). This study was a population-based prospective cohort of infants followed from birth through 6 months post-partum. Ethical approval for the study was obtained from institutional review boards at the Johns Hopkins Bloomberg School of Public Health, the Institute of Medicine at Tribhuvan University, and Cincinnati Children's Medical Center. The trial is registered at Clinicaltrials.gov (NCT01034254).

Table 1
Nepal immunization schedule during study period May 2011–April 2014.

Vaccine	Age of administration
BCG	At birth
DTP-Hib-HepB	6 weeks, 10 weeks, 14 weeks
OPV	6 weeks, 10 weeks, 14 weeks
MR	9 months
JE	12–23 months (high risk districts)
TT	During pregnancy
Vitamin A	6–59 months

2.2. Data collection

At baseline, information was collected on household structure, socioeconomic status, and demographics. At study enrollment, date of last menstrual period and pregnancy history data were collected. As soon as possible after delivery the mother and infant were visited to collect detailed birth information including infant weight and breastfeeding status. From birth through 6 months post-partum (180 days), infants were visited weekly by a field worker who recorded, based on maternal report, which specific vaccines were received in the prior 7 days. BCG is given at birth and usually results in a scar. OPV and pentavalent vaccine have the same recommended timing but differ in their administration route. The mothers reported only the type of vaccine received (not the number of the dose as this was calculated during the analysis). The field workers maintained vaccine receipt data only for the current month and therefore were not able to assess or address delays in vaccination in the field.

2.3. Analytic dataset

Infants were included in this analysis if they were followed for any length (0–180 days) during an approximately 3 year-period. Of 3693 women vaccinated, there were 3621 women with at least one live birth outcome. There were 3646 live born infants, 50 of whom were live-born twins and one live-born twin associated with a stillbirth. No weekly vaccination recall data were collected for 169 infants (~5%). The final dataset consists of 3478 infants with at least one follow-up visit during the first 6 months.

Households were categorized as crowded if 5 or more people resided in the home (median number of household members). Similarly, households were dichotomized at the median into those with >2 children under 15 years versus households with 2 or fewer children under 15 years. At enrollment women reported their literacy status (binary) and pregnancy history. For parity analysis women were categorized as nulliparous or multiparous. The field workers identified the subject's ethnicity (Pahadi – a group originating from the hills or Madeshi – a group originating from north India). Twenty-five questions were asked to develop a construct to measure the socioeconomic status of households. The questions were the following: (1–3) construction materials for ground floor, first floor, and roof, (4) number of living and sleeping rooms, (5) water source, (6) type of latrine, (7) number of servants, (8–9) number of cattle and goats, (10–11) amount of *khet* and *bari* (measures of rain fed and irrigation fed arable land owned), (12–17) number of bullock carts, bicycles, motorcycles, cars/jeeps, trucks/buses, tractors, (18–23) number of clocks, radios, televisions, satellite dishes,