NOTES

Haemophilus influenzae Type b Carriage among Young Children in Metropolitan Atlanta in the Context of Vaccine Shortage and Booster Dose Deferral

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Short-term deferral of the Haemophilus influenzae type b (Hib) vaccine booster dose during a recent U.S. Hib vaccine shortage did not result in widespread Hib carriage in Atlanta, as the Hib carriage rate was found to be 0.3% (1/342). Hib colonization was significantly more common among males and day care attendees.

Routine use of protein-polysaccharide conjugate vaccines against Haemophilus influenzae type b (Hib) led to a dramatic decline in the incidence of invasive Hib disease in the United States (1). The decline in incidence has been accompanied by the near-elimination of nasopharyngeal carriage of Hib in children <5 years of age (8), thereby inducing herd immunity.

The continued success of the U.S. Hib vaccination program was challenged during the recent U.S. Hib vaccine shortage (2). In response to the shortage, the Centers for Disease Control and Prevention (CDC) and partner organizations recommended that providers defer giving the 12- to 15-month booster dose for routine vaccinations, to ensure that the supply was sufficient for all infants to receive the primary vaccine series (2). It was predicted that short-term deferral of the booster dose would not result in an increase in Hib disease because of continued protection of infants with the primary series and the low level of nasopharyngeal carriage and transmission achieved in the United States through the Hib immunization program. However, when Hib cases presumed related to vaccine supply issues were reported in several states and it became clear that the shortage would extend longer than expected (3), we sought to determine whether the shortage was leading to an increase in Hib carriage in young children.

This Hib carriage study was embedded within a study of pneumococcal carriage (11). A random sample of children 6 months to 6 years of age who presented to the Emergency Department of Children’s Healthcare of Atlanta (CHOA) at Egleston from March to August 2009 participated in the study, with minimally exclusive criteria (English speaking, had parent/guardian consent, available at the time of the study, and not “too sick” as determined by either the emergency severity index [5] or the attending physician treating the patient).

Human subjects research approval was obtained from the Emory University and CHOA institutional review boards (IRBs).

Nasopharyngeal (NP) specimens were obtained from all study subjects by using a nylon-tipped pediatric flocked swab (Starplex; Cleveland, TN) with a flexible plastic shaft. Each swab specimen was immediately placed into a tube containing 1 ml of skim milk-tryptone-glucose-glycerine (STGG) transport medium (10). Specimens were transported at room temperature to the hospital clinical microbiology laboratory within 12 h of collection, where each tube was vortexed at high speed for 10 to 20 s and immediately frozen at −80°C. A 200-μl sample of the STGG transport medium from each specimen was transported on dry ice to the CDC Meningitis Laboratory, where isolation and characterization of Haemophilus spp. isolates were performed.

Identification of Haemophilus influenzae was based on bacterial culture and on conventional PCR (9) and real-time PCR (4, 12). Real-time PCR was performed on isolates and on DNA from all NP swab eluates. For bacterial culture, specimens were considered positive for H. influenzae if there was growth on chocolate II agar with bacitracin (Becton Dickinson, Sparks, MD) after 24 to 48 h at 37°C with 5% CO2 of oxidase-
positive, porphyrin-negative bacteria requiring NAD and heme and lacking beta-hemolysis on horse blood agar (*Haemophilus* ID Quad plates; Remel, Lenexa, KS). Bacterial isolates were further confirmed to be *H. influenzae* by the API NH system for *Neisseria* and *Haemophilus* identification (bioMérieux, Marcy l’Etoile, France). Isolates were serotyped using slide agglutination serotyping (SAST) and real-time PCR for types a to f. Additionally, 332 of 344 specimens were inoculated onto Hib antiserum agar (ASA) plates (7) and inspected for halos of precipitation around colonies, which would indicate the presence of Hib.

Differences in vaccination status by age were tested by chi-square analysis. Differences in *Haemophilus influenzae* carriage by demographic group, antibiotic use, day care attendance, and Hib vaccination were tested individually using Fisher’s exact test and in a multivariable model using logistic regression. The 342 study participants ranged in age from 6 months to 6 years (mean, 2.55 years) and were predominantly of black race (78.4%) (Table 1). Nearly half (43.6%) had used antibiotics in the past 6 months, and 48.5% attended day care at least once per week. Study subjects had a mean of 4.5 household contacts (range, 2 to 10; median, 4) as defined by parent-reported household size. Over three quarters (75.4% [258/342]) of the specimens were collected before publication of the recommendation to reinstate the booster dose (3a) and 24.6% (84/342) were collected after.

Complete Hib vaccination history was available through Georgia Registry of Immunization transactions and Services (GRITS) for 295 (86.3%) study subjects. Of the subjects with vaccine history available, 194 (65.8%) were appropriately vaccinated for age and 101 (34.2%) were un- or undervaccinated. Chi-square analysis demonstrated that there was a significant correlation between age group and vaccination status (*P* < 0.001), with un- or undervaccination being most common among 16- to 23-month-old children (59.6%) and least common among 5-year-old children (14.3%). Of the undervaccinated 16 to 23-month-olds children, 46.3% (31/67) were 12- to 15-months old during the period of booster dose deferral.

In total, 27.5% (94/342) of children were colonized with either typeable or nontypeable (NT) *H. influenzae*, ranging from 18.6% of 4 year olds to 37.5% of 5 year olds (Table 1). The vast majority (95.7%; 90/94) of *H. influenzae* carriage was due to NT strains. One unvaccinated, 31-month-old child was colonized with Hib (1/342; 0.3%; 95% confidence interval [CI], 0.3% to 1.8%) as detected by real-time PCR. Three children (0.6%) were colonized with non-b, typeable *H. influenzae*: two with type e and one with type f. *H. influenzae* colonization was significantly more common among males than females and among day care attendees than nonattendees when variables were tested individually (Table 1), and associations of sex and day care with colonization remained significant (*P* = 0.008 and *P* = 0.005, respectively) after multivariable adjustment.

| Variable | Characteristic | No. of subjects | No. (%) of subjects colonized | Distribution of *H. influenzae* serotypes among subjects | *P* value<sup>a</sup> |
|----------|----------------|-----------------|-----------------------------|---------------------------------|-------------------|
| **Age**  |                |                 |                             |                                 |                   |
| 6–15 mos |                | 88              | 21 (23.8)                   | 20 NT, 1 e                      | 0.489             |
| 16–23 mos|                | 67              | 22 (32.8)                   | 22 NT                           |                   |
| 2 yrs    |                | 59              | 15 (25.4)                   | 13 NT, 1 b, 1 c                 |                   |
| 3 yrs    |                | 58              | 18 (31.0)                   | 17 NT, 1 f                      |                   |
| 4 yrs    |                | 43              | 8 (18.6)                    | 8 NT                            |                   |
| 5 yrs    |                | 24              | 9 (37.5)                    | 9 NT                            |                   |
| 6 yrs    |                | 3               | 1 (33.3)                    | 1 NT                            |                   |
| **Sex**  |                |                 |                             |                                 |                   |
| Male     |                | 185             | 63 (34.1)                   | 61 NT, 1 b, 1 e                 | 0.004             |
| Female   |                | 157             | 31 (19.7)                   | 29 NT, 1 e, 1 f                 |                   |
| **Race/ethnicity** |         |                 |                             |                                 |                   |
| White    |                | 49              | 12 (24.5)                   | 11 NT, 1 e                      | 0.874             |
| Black    |                | 268             | 78 (29.1)                   | 75 NT, 1 b, 1 c, 1 f            |                   |
| Hispanic |                | 9               | 1 (11.1)                    | 1 NT                            |                   |
| Asian    |                | 5               | 1 (20.0)                    | 1 NT                            |                   |
| Other    |                | 10              | 2 (20.0)                    | 2 NT                            |                   |
| Unknown  |                | 1               | 0 (0.0)                     | 0                               |                   |
| **Antibiotics in past 6 mos** | |                 |                             |                                 |                   |
| No       |                | 190             | 49 (25.8)                   | 45 NT, 1 b, 2 c, 1 f            | 0.464             |
| Yes      |                | 149             | 44 (29.5)                   | 44 NT                           |                   |
| Unknown  |                | 3               | 1 (33.3)                    | 1 NT                            |                   |
| **Attends day care** |        |                 |                             |                                 |                   |
| No       |                | 175             | 37 (21.1)                   | 35 NT, 1 b, 1 e                 | 0.008             |
| Yes      |                | 166             | 57 (34.5)                   | 55 NT, 1 e, 1 f                 |                   |
| **Vaccination status**<sup>b</sup> | |                 |                             |                                 |                   |
| Unvaccinated |            | 18              | 4 (22.2)                    | 3 NT, 1 b                        | 0.222             |
| Undervaccinated |     | 83              | 28 (33.7)                   | 27 NT, 1 e                      |                   |
| Appropriately vaccinated | | 194             | 54 (27.8)                   | 53 NT, 1 e                      |                   |
| Incomplete information | | 47              | 8 (17.0)                    | 7 NT, 1 f                        |                   |

<sup>a</sup> *P* values for each variable were determined using Fisher’s exact test.

<sup>b</sup> A subject was considered undervaccinated for age if he or she was 6 to 15 months old and had received less than 3 doses of PRP-T or any combination of vaccine type or less than 2 doses of PRP-OMP vaccine. A subject was considered undervaccinated if older than 15 months and received less than 4 doses of PRP-T or a combination of vaccine type or less than 3 doses of PRP-OMP.
Culture results also yielded *Haemophilus parainfluenzae* (n = 8), *Haemophilus haemolyticus* (n = 1), *Moraxella catarrhalis* (n = 13), *Neisseria lactamica* (n = 1), *Neisseria polysacchara-rea/Neisseria spp.* (n = 8), and isolates unidentifiable by NH strip (n = 3). Twenty-three (23/122; 18.9%) isolates were positive for β-lactamase with the NH system: 12/88 NT *H. influenzae*, 10/13 *M. catarrhalis*, and 1/8 *Neisseria spp.*

Hib carriage was detected in 0.3% of this study population, a single unvaccinated child, which is consistent with a study of Hib carriage among children presenting to emergency departments in the Atlanta area in 1993, after implementation of the Hib conjugate vaccine program (8). Our results also concur with those of a February 2009 Minnesota carriage survey, in which no Hib was recovered (6). Hib was not detected by comparison with those of a February 2009 Minnesota carriage survey, in which no Hib was recovered (6). Hib was not detected by culture in this or the two previous studies; however, compared to culture in this study, real-time PCR (4, 12) did detect one additional Hib carrier and *H. influenzae* from 6 culture-negative NP swab eluates.

In conclusion, deferral of the Hib vaccine booster dose between December 2007 and June 2009 did not result in a measurable short-term increase in Hib carriage in children ≤6 years of age in Atlanta, compared to a prior study of this population, a finding which supports the 2007 interim recommendation (2) to defer the booster dose and suggests that children remained protected by the cushion of herd immunity during the 18-month vaccine shortage. However, these findings may not accurately portray Hib carriage if the booster dose were to be deferred for a longer term.

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