Seroprevalence of Measles, Rubella, Tetanus, and Diphtheria Antibodies among Children in Haiti, 2017

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Abstract. In Haiti, measles, rubella, and maternal and neonatal tetanus have been eliminated, but a diphtheria outbreak is ongoing as of 2019. We conducted a nationally representative, household-based, two-stage cluster survey among children aged 5–7 years in 2017 to assess progress toward maintenance of control and elimination of selected vaccine-preventable diseases (VPDs). We stratified Haiti into West region (West department, including the capital city) and non-West region (all other departments). We obtained vaccination history and dried blood spots, and measured antibody concentrations to VPDs on a multiplex bead assay. Among 1,146 children, national seropositivity was 83% (95% CI: 80–86%) for tetanus, 83% (95% CI: 81–85%) for diphtheria, 87% (95% CI: 85–89%) for measles, and 84% (95% CI: 81–87%) for rubella. None of the children had long-term immunity to tetanus or diphtheria (IgG concentration ≥ 1 international unit/mL). Seropositivity in the West region was lower than that in the non-West region. Vaccination coverage was 68% (95% CI: 61–74%) for ≥ 3 doses of tetanus- and diphtheria-containing vaccine (DTP3), 84% (95% CI: 80–87%) for one dose of measles–rubella vaccine (MR1), and 20% (95% CI: 16–24%) for MR2. The seroprevalence of measles, rubella, and diphtheria antibodies is lower than population immunity levels needed to prevent disease transmission, particularly in the West region; reintroduction of these diseases could lead to an outbreak. To maintain VPD control and elimination, Haiti should achieve DTP3 and MR2 coverage $\geq 95\%$, and include tetanus and diphtheria booster doses in the routine immunization schedule.

INTRODUCTION

An essential function of national immunization programs is to routinely estimate vaccination coverage to evaluate performance and assess progress toward and maintenance of vaccine-preventable disease (VPD) control and elimination. Serosurveys measuring antibody responses to VPDs offer an objective measure of population immunity that can be useful to identify immunity gaps, monitor progress toward VPD elimination, investigate causes of disease resurgence, and, in certain settings, estimate vaccination coverage.^{1–3} The immune response to vaccination depends on several factors, including the individual's humoral and cellular immune system, age at vaccination, type of vaccine (live versus inactivated), and number of doses received.^{1,4}

Haiti's national immunization program has made significant progress toward the Pan American Health Organization (PAHO) regional VPD elimination goals. The last confirmed measles and rubella cases occurred in 2001 and 2006, respectively,⁵ and measles and rubella/congenital rubella syndromes were verified to be eliminated in 2014.⁶ Maternal and neonatal tetanus were verified to be eliminated in 2017.^{7,8} However, a diphtheria outbreak started in Haiti in 2014⁹ and continues as of December 2019.^{10,11} In addition, Haiti has not reached the vaccination coverage targets recommended by the PAHO.^{12,13}

Three doses of diphtheria–tetanus–pertussis containing vaccine (DTP) at 6, 10, and 14 weeks, and one dose of measles–rubella vaccine (MR) at 9 months are recommended in the routine vaccination schedule. Diphtheria toxoid and tetanus toxoid are the antigens of interest in this survey. Measles–rubella vaccination campaigns targeting children aged 9 months to 9 years and 9–59 months were conducted in 2012 and 2016, respectively.⁶ A second dose of MR at 13 months of age was introduced in 2016.¹⁴ A booster dose of DTP has been recommended for children aged 15 months since the 1980s, except 2012–2015 because of financial constraints.

Data on measles, rubella, diphtheria, and tetanus immunity among children in Haiti are unknown and are needed to evaluate progress toward maintaining elimination and preventing epidemics. We conducted this survey to estimate immunity to these VPDs among children aged 5–7 years at the time of the survey. We compared serologic results with survey estimates of DTP and MR coverage.

MATERIALS AND METHODS

Design and sampling. The survey was a nationally representative, household-based, stratified, two-stage cluster survey conducted in November 2017. The survey was designed to estimate chronic hepatitis B virus (HBV) infection and immunity to diphtheria, tetanus, measles, and rubella. Haiti was stratified into West region, which contains the West department (including the urban metropolitan Port-au-Prince, where 1/3 of Haiti's population lives),¹⁵ and non-West region (all other departments). The primary and secondary sampling units were 78 enumeration areas (EAs) per region, selected by

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probability proportional to size, and 62 households per EA, selected by simple random sampling. A total of 4,836 households were targeted with the goal to recruit at least 455 children aged 5–7 years per region. For EAs containing 62 or fewer households, all households were included in the survey. During the survey, the teams conducted two revisits to a household before determining that a household was unoccupied or that an eligible child did not live in the household. If more than one eligible child was present, then one child was selected by simple random sampling. Children were included in the survey if the caregiver gave consent for the child's participation. Further details of age selection, sampling, and the sample size calculation, which were based on the estimated HBV infection prevalence, are reported elsewhere.¹⁶

Data collection. A questionnaire was administered to caregivers, which included questions about household composition, caregiver's demographics and socioeconomic characteristics, child's demographics and education level, and child's vaccination status. Caregivers were asked to present all cards from routine vaccination visits and campaigns.

At least three drops of blood were collected by finger prick onto TropBio filter wheels (Cellabs, Sydney, Australia). The blood spots were dried in the field (creating dried blood spots [DBS]), and then transported to the National Public Health Laboratory in Port-au-Prince, where they were stored in the freezer at -40°C . Dried blood spots were analyzed at the CDC Atlanta.

Laboratory methods and analysis. *Corynebacterium diphtheriae* toxoid (List Biological Laboratories, Campbell, CA), tetanus toxoid (Massachusetts Biological Laboratories, Boston, MA), and recombinant measles virus N (MVN) protein (Meridian Life Sciences, Memphis, TN) were purchased from the indicated sources. Recombinant MVN protein from insect cell expression was partially purified by MonoQ HR5/5 column chromatography (GE Healthcare, Piscataway, NJ) in buffer containing 25 mM Tris at pH 8.0. Measles virus N protein was eluted from the column between 0.5 and 1.0 M NaCl and was dialyzed (Spectra Por-3 tubing, Spectrum Laboratories, Rancho Dominguez, CA) into buffer containing 10 mM NaH_2PO_4 at pH 7.2 with 0.85% NaCl (phosphate-buffered saline [PBS]). Bead coupling conditions have been described elsewhere.^{17,18} Because the magnetic beads are larger than the previously used SeroMap beads, the protein amounts were increased by 15%; 14.4 μg of tetanus toxoid, 69 μg of diphtheria toxoid, and 6.9 μg of measles protein were used to couple 12.5×10^6 magnetic beads in a 1-mL final volume. Inactivated whole rubella virus (Meridian Life Sciences, grade 4) was coupled using 34.5 μg for 12.5×10^6 magnetic beads in 1 mL of buffer containing 50 mM 2-(N-morpholino)ethanesulfonic acid at pH 5.0 and 0.85% NaCl.

For each specimen, a single 6-mm punch of DBS was eluted in buffer B (PBS containing 0.5% bovine serum albumin [BSA], 0.3% Tween-20, 0.1% casein, 0.02% sodium azide, 0.5% polyvinyl alcohol, 0.8% polyvinylpyrrolidone, and 3 $\mu\text{g}/\text{mL}$ *E. coli* extract) by incubation overnight at 4°C . A final dilution of 1:200 whole blood (equivalent to 1:400 serum dilution with 50% hematocrit assumption in whole blood) was prepared in buffer B, and specimens were stored at 4°C until analysis.

For the detection of IgG antibodies against the antigens coupled to microbeads, the multiplex bead assay (MBA) was performed as described previously¹⁹ in flat bottom Bio-Plex Pro 96-well plates (Bio-Rad, Hercules, CA), with specimens

run in duplicate. Washes between incubation steps used a handheld magnet (Luminex Corp, Austin, TX). Beads (250,000 beads/antigen/plate) were suspended in buffer A (PBS, 0.5% BSA, 0.05% Tween-20, and 0.02% NaN_3), and 50 μL of bead mastermix was added to each well. After addition of 200 μL wash buffer (PBS, 0.05% Tween-20; [PBST]) to each well, wash buffer was left in each well for one minute to allow bead magnetization before inverting the plate to evacuate the wells of liquid. Plates were washed two times with PBST, and 50 μL of specimen (at 1:200 whole blood dilution) was added to each well and incubated with shaking at room temperature for 90 minutes. After three washes with PBST, beads were incubated with biotinylated antihuman IgG (1:500, Southern Biotech, Birmingham, AL) and biotinylated antihuman IgG₄ (1:625, Southern Biotech). Then, plates were incubated for 45 minutes and washed three times with PBST. Streptavidin conjugated to phycoerythrin (PE) (1:200, Invitrogen, Waltham, MA) was added to detect bound secondary antibody. After a 30-minute incubation, wells were washed three times with PBST and incubated in buffer A for 30 minutes under light shaking to remove any loosely bound antibodies. Specimens were resuspended in 100 μL PBS, and fluorescence data were collected immediately on the MAGPIX with Bio-Plex Manager™ software 6.1 (Bio-Rad, Hercules, CA) with a target of 50 beads per region per well. Median fluorescence intensity (MFI) signal was generated for a minimum of 50 beads/region, and background MFI from wells incubated with buffer B was subtracted from each specimen to give a final value of MFI minus background (MFI-bg) for analysis.

Serial dilutions of reference serum standards from the WHO International Laboratory for Biological Standards were made for tetanus (TE-3; 120 international units/mL [IU/mL]), rubella (67/182; 80 IU/mL), and diphtheria (10/262; 2 IU/mL). These dilution series were run under the same assay conditions listed earlier and on the same MAGPIX machine as the unknown specimens. Regression curves for each standard were produced to translate an unknown specimen's MFI-bg assay signal value to an IgG concentration of IU/mL serum. A reference standard for the measles virus plaque reduction neutralization test (PRNT²⁰; 3 IU/mL) is available for the quantitation of total virus-neutralizing antibody responses, but the standard has not been calibrated for use in ELISA format. Because only IgG antibodies to the MVN protein are detected in our multiplex assay, a ROC-optimized MFI-bg cutoff value that provided good sensitivity and specificity compared with the "gold standard" PRNT was determined (Coughlin et al., unpublished).¹⁸ This value was translated to the magnetic bead set used in this work and was determined to be 314 MFI-bg units.

Seropositivity for tetanus, diphtheria, and rubella antibodies was defined by extrapolated IU/mL antibody concentration. Tetanus and diphtheria antibody seropositivities were defined using the standard cutoff of 0.01 IU/mL.^{21–24} Tetanus and diphtheria antibody seropositivities were further categorized as IgG < 0.01 IU/mL, 0.01 to < 0.1 IU/mL, 0.10 to < 1 IU/mL, and ≥ 1 IU/mL.^{17,23} These categories are associated with a lack of protection, minimal protection, full protection, and long-term protection against diphtheria.²¹ Increasing antibody concentrations against tetanus are associated with a decreased risk of infection and longer term protection,²² and tetanus antibody concentrations ≥ 1 IU/mL are associated with long-term protection.^{25,26} Rubella antibody seropositivity was defined

as ≥ 10 IU/mL.²⁷ Measles antibody seropositivity was defined as 314 MFI-bg units, as described previously.

Statistical analysis. Data from the questionnaires were entered into a Microsoft Access (Microsoft Corp., Redmond, WA) database and analyzed using SAS 9.4 (The SAS Institute, Cary, NC). Descriptive analyses of demographic and socioeconomic characteristics were calculated. Seroprevalence and vaccination coverage estimates, both nationally and for the West and non-West regions, were calculated, accounting for survey design, which included strata, cluster, and weight statements. The SAS statements and survey weight calculations used in this survey are described elsewhere.¹⁶ The number of card-documented doses and dates of vaccination (if noted on card) with any diphtheria-tetanus-pertussis containing vaccine (DTP) and MR was noted. Diphtheria-tetanus-pertussis containing vaccine was recorded as DTP1–4+ (DTP doses 1–4 or more), and MR coverage from routine or campaign cards was combined and recorded as MR1 and MR2+. For children without a card, caregiver recall was used to determine vaccination status. If the caregiver answered “I don’t know” to whether the child received any doses or to the number of doses, the child was coded as missing vaccination data. Vaccination coverage estimates by card documentation and caregiver recall were combined to determine coverage by either source.

Diphtheria-tetanus-pertussis containing vaccine 3+ and MR2+ were considered fully vaccinated because the children had been eligible for three doses of DTP through the routine system and two doses of MR through the routine system plus campaigns. The median time to vaccination was assessed using survival analysis among children with dates on their routine vaccination card, and results were displayed with Kaplan–Meier curves, highlighting timely vaccination (within 2 weeks for DTP1 and DTP3 and 1 month for MR1). Measles-rubella vaccine 2 timeliness was not calculated because MR2 was introduced into the routine immunization program in 2016.

Rao–Scott chi-square tests were used to determine associations between demographic and socioeconomic factors with antibody seropositivity and vaccination coverage, and to compare vaccination coverage to antibody seropositivity. A *P*-value of < 0.05 was considered statistically significant for all tests.

Ethics/human subjects. The National Bioethics Committee in Haiti and the PAHO Ethics Review Committee reviewed and approved the protocol. The Human Subjects Protection Office at the CDC reviewed the protocol, and the protocol did not require review by the Institutional Review Board.

RESULTS

General characteristics. During the household enumeration, some EAs contained fewer than 62 households, so a total of 4,736 households were identified for inclusion in the survey. Of 4,736 households, contact was made at 4,587 (97%) households during the survey, and 1,181 households (26%) of the 4,587 households included at least one child aged 5–7 years. Among 1,181 children identified for potential enrollment, 1,152 (98%) caregivers provided consent. Of the 1,152 children included in the survey, 1,146 (99%) had enough DBS specimen to be included in the analyses. Of the 1,146 children included in the survey, 524 (46%) lived in the West region and 622 (54%) lived in the non-West region. Among children, 50% were male and 62% were in primary school. Among the

children’s caregivers, 75% had a job and 33% had at least some secondary school education (Table 1). Characteristics of the children and their caregivers were similar by region, except that caregivers in the West region had a higher education level than caregivers in the non-West region ($P = 0.01$).

Seropositivity. Nationally, the weighted seropositivity among children aged 5–7 years in Haiti in 2017 was 83% (95% CI: 81–85%) for diphtheria antibody, 83% (95% CI: 80–86%) for tetanus antibody, 84% (95% CI: 81–87%) for rubella antibody, and 87% (95% CI: 85–89%) for measles antibody (Table 2). Seropositivity for diphtheria, tetanus, and measles antibodies was significantly lower in the West region than in the non-West Region. Seropositivity against rubella was lower in the West region, but the difference was not statistically significant (Table 2). None of the enrolled children had tetanus or diphtheria IgG concentrations ≥ 1.0 IU/mL (Table 2). When comparing antibody seropositivity with each component of the combination vaccines, 8% (95% CI: 6–11%) of children were immune to tetanus only, 9% (95% CI: 7–11%) were immune to diphtheria only, 75% (95% CI: 71–77%) were immune to both, and 9% (95% CI: 7–11%) were susceptible to both. Furthermore, 6% (95% CI: 5–9%) of children were immune to measles only, 3% (95% CI: 2–4%) were immune to rubella only, 81% (95% CI: 78–84%) were immune to both, and 10% (95% CI: 8–12%) were susceptible to both.

Vaccination coverage. Of 1,146 enrolled children, 552 (49%) had a routine vaccination card available, 145 (13%) had a campaign card from the 2012 and/or 2016 campaigns, and 603 (54%) had either a routine or campaign card. There was no difference among children from the West and non-West regions regarding card availability ($P = 0.8$). Few children had both routine and campaign cards (94/1,146, 8%). For children without vaccination cards, the caregivers were most likely to report that the card was in another location (48%) or that the caregiver lost the card (43%). Diphtheria-tetanus-pertussis containing vaccine or MR status was unknown for 186 (16%) and 177 (15%) participants, respectively. Diphtheria-tetanus-pertussis vaccine coverage by card or recall was as follows: DTP1 91% (95% CI: 87–94%), DTP2 84% (95% CI: 78–88%), DTP3 68% (95% CI: 61–74%), and DTP4+ 34% (95% CI: 30–39%). Measles-rubella vaccine 1 coverage by card or recall was 84% (95% CI: 80–87%), and MR2+ coverage was 20% (95% CI: 16–24%). There was no difference in vaccination coverage between the West and non-West regions (Table 3).

Of 552 children with cards, vaccination dates were available for 515 (93%) for DTP1, 465 (84%) for DTP3, and 451 (82%) for MR1. The median time to receipt of DTP1 was 10 weeks, DTP3 was 27 weeks, and MR1 was 12 months (Supplemental Figure 1).

Seropositivity and vaccination coverage. Tetanus and diphtheria antibody seropositivities (83%) were higher than DTP3+ coverage (68%) by card or recall. Measles antibody seropositivity (87%) was higher than and rubella antibody seropositivity (84%) was similar to MR1+ coverage (84%) by card or recall (Figure 1). The proportion of children who were seropositive for each VPD increased with increasing numbers of vaccination doses by card or recall. Among children who received at least three doses of DTP by card or recall, seropositivity was 88% for diphtheria antibody and 89% for tetanus antibody. Among children who received at least two doses of MR by card or recall, seropositivity was 89% for measles antibody and 87% for rubella antibody (Table 4).

TABLE 1
Demographic and socioeconomic characteristics of surveyed children aged 5–7 years and their caregivers—Haiti, 2017

Characteristic	Total, N = 1,146		West region, N = 524		Non-west region, N = 622	
	n	%	N	%	N	%
Gender of child*						
Male	570	49.8	269	51.4	301	48.4
Female	575	50.2	254	48.6	321	51.6
Age of child (years)						
5	353	30.8	150	28.6	203	32.6
6	410	35.8	207	39.5	203	32.6
7	383	33.4	167	31.9	216	34.7
Education level of child*						
None	42	3.7	22	4.2	20	3.2
Kindergarten/preschool	390	34.1	188	36.0	202	32.5
Primary	712	62.2	312	59.8	400	64.3
Age of caregiver (years)*						
< 30	316	27.6	135	25.8	181	29.1
30–39	463	40.4	233	44.6	230	37.0
≥ 40	366	32.0	155	29.6	211	33.9
Caregiver has a job*	853	74.6	378	72.3	475	76.5
Education level of caregiver						
None	219	19.1	78	14.9	141	22.7
Some or completed primary	451	39.4	164	31.3	287	46.1
Some secondary	372	32.5	207	40.0	165	26.5
Completed secondary or higher	104	9.1	75	14.3	29	4.7

* Data missing from some questionnaires.

A sensitivity analysis was performed among children with cards to investigate whether card coverage would more accurately reflect immunity than recall. Immunity by vaccination status was similar for all antigens whether measured by card only or card and recall. For tetanus immunity, there were only 16 children with cards who had no documentation of tetanus vaccination, and, of these children, 54% (95% CI: 30–76%) were immune to tetanus (Table 4).

DISCUSSION

This survey is the first to estimate immunity against diphtheria, tetanus, measles, and rubella among children in Haiti and provides important data for Haiti's immunization program.

None of the children showed evidence of long-term protection against tetanus or diphtheria, which supports the biologic finding that immunity wanes over time in the absence of tetanus and diphtheria booster doses.^{21,22,28,29} Maternal and neonatal tetanus elimination has been achieved in Haiti, but long-term immunity is needed to sustain elimination. The lack of long-term protection is concerning because, according to national coverage surveys, DTP3 coverage in Haiti has fallen from 63% to 55% from 2012 to 2017.³⁰ According to the World Health Organization-United Nations Children's Fund (WHO-UNICEF) vaccination coverage estimates, DTP3 coverage was only 64% in 2018.¹² In addition, the vaccination coverage estimates for all antigens in Haiti, such as third-dose polio vaccine (64% in 2018),¹² are low, which raises concerns for control and elimination of other VPDs.

TABLE 2
Seropositivity for diphtheria, tetanus, measles, and rubella among children aged 5–7 years—Haiti, 2017*

Disease (immunity threshold)	Total, N = 1,146		West region, N = 524		Non-west region, N = 622		P-value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
Diphtheria (≥ 0.01 IU/mL)	934	83.1 (80.7–85.4)	390	75.1 (70.5–79.1)	544	87.5 (84.5–90.0)	< 0.001
Tetanus (≥ 0.01 IU/mL)	930	82.7 (79.5–85.5)	396	75.7 (69.0–81.3)	534	86.5 (83.1–89.4)	< 0.01
Rubella (≥ 10 IU/mL)	943	84.0 (80.5–86.9)	411	79.9 (73.8–84.9)	532	86.1 (81.9–89.4)	0.07
Measles (≥ 314 Median fluorescence intensity minus background)	975	87.4 (85.1–89.3)	410	80.2 (75.1–84.5)	565	91.2 (88.7–93.2)	< 0.001
Diphtheria immunity categories (IU/mL)†							
< 0.01	212	16.9 (14.6–19.3)	134	24.9 (20.9–29.5)	78	12.5 (10.0–15.5)	< 0.001
0.01 to < 0.1	559	48.4 (43.8–52.9)	257	48.4 (42.5–54.4)	302	48.3 (42.3–54.4)	–
0.1 to < 1	375	34.8 (30.4–39.4)	133	26.6 (21.6–32.4)	242	39.2 (33.3–45.4)	–
≥ 1	0	0	0	0	0	0	–
Tetanus immunity categories (IU/mL)†							
< 0.01	216	17.3 (14.5–20.5)	128	24.3 (18.7–31.0)	88	13.5 (10.6–16.9)	< 0.01
0.01 to < 0.1	373	32.6 (29.2–36.3)	160	31.6 (26.8–36.7)	213	33.2 (28.6–38.2)	–
≥ 0.1 to < 1	557	50.1 (45.8–54.4)	236	44.1 (38.4–50.0)	321	53.3 (47.7–58.9)	–
≥ 1	0	0	0	0	0	0	–

* Percentages account for strata, cluster, and weight.

† This section compares the proportion of children in each immunity category between the West and non-West regions.

TABLE 3
Vaccination coverage by source of information among children aged 5–7 years—Haiti, 2017*

	Total		West region		Non-west region		P-value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
DTP1†							
Vaccination card	536	57.1 (51.1–62.8)	241	57.0 (47.9–65.6)	295	57.1 (49.5–64.4)	1.0
Caregiver report	321	33.7 (29.4–38.2)	141	30.9 (25.5–36.8)	180	35.1 (29.4–41.3)	0.3
Either source	857	90.8 (87.0–93.5)	382	87.9 (81.3–92.3)	475	92.2 (87.5–95.3)	0.2
DTP2							
Vaccination card	512	55.3 (49.1–61.3)	231	55.4 (46.6–64.0)	281	55.2 (47.0–63.0)	1.0
Caregiver report	263	28.3 (24.6–32.4)	120	27.0 (22.0–32.1)	143	29.2 (24.2–34.7)	0.5
Either source	775	83.6 (78.2–87.8)	351	82.1 (74.8–87.7)	424	84.3 (77.0–89.7)	0.6
DTP3							
Vaccination card	480	52.0 (45.4–58.5)	218	51.3 (42.2–60.4)	262	52.4 (43.7–60.9)	0.9
Caregiver report	153	15.5 (12.8–18.8)	72	15.9 (12.2–20.4)	81	15.3 (11.8–19.7)	0.8
Either source	633	67.5 (60.8–73.6)	290	67.2 (56.1–76.4)	343	67.7 (59.2–75.2)	0.9
DTP4+							
Vaccination card	239	25.7 (21.6–30.3)	115	26.5 (20.3–33.9)	124	25.2 (20.1–31.2)	0.8
Caregiver report	77	8.4 (6.2–11.1)	33	7.5 (5.3–10.7)	44	8.8 (6.0–12.7)	0.6
Either source	316	34.0 (29.7–38.6)	148	34.1 (27.5–41.4)	168	34.0 (28.6–40.0)	1.0
MR1‡							
Vaccination card	525	55.0 (50.0–60.0)	236	55.7 (47.1–64.0)	289	54.7 (48.4–60.8)	0.8
Caregiver report	272	28.7 (25.0–32.8)	110	24.5 (20.7–28.8)	162	30.9 (25.6–36.7)	0.07
Either source	797	83.7 (80.0–86.9)	346	80.2 (71.6–86.7)	451	85.5 (81.9–88.6)	0.2
MR2+							
Vaccination card	86	8.6 (6.5–11.4)	45	10.4 (6.6–16.0)	41	7.7 (5.3–11.1)	0.3
Caregiver report	109	11.3 (8.9–14.3)	48	11.4 (8.4–15.3)	61	11.2 (8.1–15.4)	0.9
Either source	195	20.0 (16.2–24.1)	93	21.8 (17.0–27.6)	102	18.9 (14.2–24.7)	0.4

* Percentages account for strata, cluster, and weight.

† DTP = any diphtheria-tetanus-pertussis containing vaccine. For DTP, 186 (16%) participants were missing both card and caregiver report information (no card and caregiver answered “I don’t know” to recall questions); therefore, denominators are as follows: total (N = 960), West region (N = 434), and non-West region (N = 526).

‡ MR = measles-rubella vaccine. MR1 and MR2+ include MR doses from the routine system and/or campaigns. For MR, 177 (15%) participants were missing both card and caregiver report information; therefore, denominators are as follows: total (N = 969), West region (N = 436), and non-West region (N = 533).

In this survey, diphtheria immunity among children aged 5–7 years was 83% overall and 75% in the West region, which may not have reached the level needed for herd protection (80–85%).³¹ Reviews of diphtheria cases in Haiti found that most cases were unvaccinated or incompletely vaccinated, and school-aged children have been disproportionately affected.^{9,32} In the current survey, 9% of children were immune to diphtheria and not tetanus, which could mean that they were exposed to the diphtheria toxin through natural infection. In response to the epidemic, the Ministry of Public Health and Population launched a vaccination campaign during March–April 2018, and, 1 month after the first phase of the campaign, the number of diphtheria cases and deaths decreased.³³ Data from the current survey and the diphtheria outbreak, combined with Haiti’s low DTP3 coverage, support the need to achieve DTP3 coverage of 95%, achieve high coverage of DTP4, and introduce tetanus- and diphtheria-containing booster doses for children aged 4–7 years and 9–15 years in Haiti’s routine schedule as per WHO and PAHO recommendations.^{13,34}

For rubella, the national and West region-specific seroprevalence estimates were lower than the 85–87% minimum levels needed for herd protection.³⁵ For measles, the national and regional seroprevalence estimates were lower than the minimum herd protection levels of 89–94%.³⁶ These findings are concerning because the country is at risk of an epidemic if either disease were to be introduced into the country. After the 2012 MR campaign for children aged 1–9 years, a coverage survey found that 31% of children received their first dose of MR during the campaign, which emphasizes the role of vaccination campaigns in reaching children who were missed during routine vaccination.⁵ Haiti’s routine MR1 coverage has

declined from 65% in 2012 to 61% in 2017, according to national vaccination coverage surveys.^{30,37} In 2018, MR2 coverage was only 38% according to WHO–UNICEF vaccination coverage estimates.¹² The measles and rubella immunity data from this survey support the PAHO and WHO recommendations that countries should achieve ≥ 95% coverage with two doses of MR vaccine through the routine immunization system, and that measles-containing vaccine immunization campaigns may be indicated if the routine system has not reached high coverage.^{36,38} Considering the findings of this survey, it may be useful to conduct an immunization campaign with MR and age-appropriate tetanus- and diphtheria toxoid-containing vaccine.

The antibody seroprevalence against all four VPDS was lower in the West region than in the non-West region. Vaccination coverage surveys have shown lower coverage from routine immunization services and campaigns in the West department/Port-au-Prince area,^{5,30,37} which could be due to difficulties reaching children in urban areas.^{39,40} Before measles elimination, an international measles importation led to an outbreak in Haiti, particularly in Port-au-Prince,⁵ which is further evidence that the West department is at risk of an epidemic. The immunity gap in the West region suggests that additional interventions should take place to improve vaccination coverage in Port-au-Prince.

This serosurvey highlighted benefits of using serosurvey data in addition to vaccination coverage data. Diphtheria-tetanus-pertussis containing vaccine 3 coverage by card or recall underestimated seropositivity (83%) for diphtheria and tetanus antibodies. Some children who did not receive any doses of DTP based on card documentation were immune to tetanus, which could only occur after vaccination.²² Surveys

FIGURE 1. Vaccination coverage and seropositivity among children aged 5–7 years old—Haiti, 2017. Numbers represent point estimates, brackets represent 95% CI. Tetanus and diphtheria vaccination coverage and seropositivity among children aged 5–7 years—Haiti, 2017. (B) Measles and rubella vaccination coverage and seropositivity among children aged 5–7 years—Haiti, 2017.

using card documentation or recall to assess vaccination coverage are at risk of information and recall bias, and both card documentation and recall have been found to underestimate actual DTP coverage or immunity.^{17,41,42} In addition, almost 20% of children were excluded from the vaccination coverage estimates because they were missing vaccination cards, and their caregiver did not remember whether the child had been vaccinated. Many of these children might have been vaccinated, leading to higher seroprevalence than vaccination

coverage. In this survey, 8% of children were immune to tetanus and not diphtheria, which indicates that the children were most likely vaccinated against diphtheria and tetanus, but their diphtheria immunity had already waned by the time of the survey. Measles–rubella vaccine 2+ coverage was likely underestimated in the current survey because all children were eligible for at least two MR doses through the routine system and at least one of the campaigns. An MR vaccination coverage survey conducted after the 2012 MR campaign estimated

TABLE 4
Seropositivity for diphtheria, tetanus, measles, and rubella by vaccination status among children aged 5–7 years—Haiti, 2017*

Vaccination status (card or recall)†	Diphtheria immune (≥0.01 IU/mL)			Tetanus immune (≥0.01 IU/mL)			Rubella immune (≥10 IU/mL)			Measles immune (≥314 Median fluorescence intensity minus background)		
	n	N	P-value	n	N	% (95% CI)	n	N	% (95% CI)	n	N	% (95% CI)
Unvaccinated	66	103	0.001	56	103	59.7 (45.4–72.5)	110	172	67.5 (56.6–76.8)	120	172	73.5 (63.9–81.3)
Partial	180	224	–	164	224	74.8 (67.1–81.1)	526	602	87.8 (82.6–91.7)	536	602	90.6 (88.0–92.6)
Complete	549	633	–	565	633	89.4 (85.8–92.1)	167	195	86.8 (81.2–90.9)	171	195	89.2 (84.0–92.9)
Vaccination status (card only)†												
Unvaccinated	11	16	0.1	9	16	53.9 (29.9–76.2)	57	78	73.7 (60.7–83.6)	58	78	74.6 (63.0–83.5)
Partial	46	56	–	45	56	84.0 (72.2–91.3)	400	439	90.3 (84.8–94.0)	405	439	93.1 (90.3–95.1)
Complete	425	480	–	440	480	90.7 (87.0–93.4)	80	86	90.5 (82.4–95.1)	81	86	91.6 (81.2–96.5)

* Percentages account for strata, cluster, and weight.
† Unvaccinated = no doses documented by card or recall. For tetanus and diphtheria toxoid containing vaccines, partial vaccination is one or two doses and complete vaccination is at least three doses. For MR, partial vaccination is one dose and complete vaccination is two doses.

MR2+ coverage of 45.7% (95% CI: 41.8–49.7%) and 27.2% (95% CI: 23.1–31.2%) for children born in 2010 and 2011, respectively,⁵ compared with 20% MR2+ coverage in the current survey, which included children born in those years. In addition, the 2016 MR campaign had 99% coverage based on administrative data.⁴³ The difference in coverage between the different surveys and seroprevalence data is likely due to the low card retention in the current survey and decreasing caregiver recall over time.

There are some limitations if serosurveys are used without vaccination coverage surveys. For diphtheria, measles, and rubella, immunity reflects either vaccination or previous infection; therefore, seroprevalence data alone cannot distinguish these scenarios.⁴ Antibody seroprevalence does not necessarily correlate with the number of doses of vaccines received,¹ or vaccine timeliness, which are important indicators for the immunization program. In this survey, the median time to DTP3 and MR was 13 weeks and 3 months later, respectively, than recommended, which is similar to findings from a previous vaccination coverage survey in Haiti.⁴⁴ It is also possible that the MBA could detect non-neutralizing antibodies to diphtheria; however, studies have shown that the MBA performs well compared with the gold standard Vero cell test.^{45,46}

This survey provides the first estimates of immunity to diphtheria, tetanus, measles, and rubella among children in Haiti. The findings highlight the need to attain ≥95% DTP3 and MR2 coverage nationally, particularly in the metropolitan Port-au-Prince area, and to introduce tetanus- and diphtheria toxoid-containing booster doses for children aged 4–7 years and 9–15 years and sustain high coverage of booster doses. The survey results also highlight the benefit of supplementing vaccination coverage data with seroprevalence data to provide a better assessment of the vaccination program and identify immunity gaps. Without achieving high vaccination coverage and adequate booster doses as per the WHO-recommended schedule, Haiti risks reestablishment of measles or rubella, an increase in maternal and neonatal tetanus cases, and ongoing diphtheria epidemics.

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