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Factors associated with incomplete vaccination and negative antibody test results for measles, mumps, and hepatitis A among children followed in the MINA-BRAZIL cohort

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ABSTRACT

Vaccination coverage has been dropping in Brazil and other countries. In addition, immune responses after vaccination may not be homogeneous, varying according to sociodemographic and clinical factors. Understanding the determinants of incomplete vaccination and negative antibody test results may contribute to the development of strategies to improve vaccination effectiveness. In this study, we aimed to investigate the frequency of vaccine adherence, factors associated with incomplete vaccination for measles, mumps, rubella (MMR) and hepatitis A, and factors associated with the seronegative test results for measles, mumps and hepatitis A at 2 years of age. This was a population-based cohort that addressed health conditions and mother/infant nutrition in Cruzeiro do Sul city, Brazil. Vaccination data were obtained from official certificates of immunization. The children underwent blood collection at the two-year-old follow-up visit; the samples were analyzed using commercially available kits to measure seropositivity for measles, mumps, and hepatitis A. We used modified Poisson regression models adjusted for covariates to identify factors associated with incomplete vaccination and negative serology after vaccination. Out of the 825 children included in the study, adherence to the vaccine was 90.6% for MMR, 76.7% for the MMRV (MMR + varicella), and 74.9% for the hepatitis A vaccine. For MMR, after the adjustment for covariates, factors associated with incomplete vaccination included: white-skinned mother; paid maternity leave; raising more than one child; lower number of antenatal consultations; and attending childcare. For hepatitis A, the factors included: white-skinned mother and not having a cohabiting partner. The factors with statistically significant association with a negative antibody test result included: receiving Bolsa Familia allowance for measles and mumps; incomplete vaccination for measles; and vitamin A deficiency for mumps. Strategies to improve the efficiency of vaccine programs are urgently needed. These include improvements in communication about vaccine safety and efficacy, and amplification of access to primary care facilities, prioritizing children exposed to the sociodemographic factors identified in this study. Additionally, sociodemographic factors and vitamin A deficiency may impact the immune responses to vaccines, leading to an increased risk of potentially severe and preventable diseases.

KEYWORDS: Vaccines. Measles. Mumps. Hepatitis A. Antibodies.

INTRODUCTION

The establishment of the National Immunization Program (Programa Nacional de Imunizacao - PNI) by the Ministry of Health in 1973 was an important public health development in Brazil. The PNI is responsible for planning and implementing the national vaccination calendar, aiming to control vaccine-preventable diseases[1]. Some

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relevant achievements following the establishment of the PNI include the eradication of poliomyelitis and remission of sustained transmission of rubella in the country[2].

Currently, the PNI offers free-of-charge vaccination for all 19 vaccines recommended by the World Health Organization (WHO), according to the national vaccination calendar. The vaccine against measles, mumps and rubella (MMR) is included in the pediatric calendar in a 2-dose regimen at 12 months and 15 months; the second dose is usually given in combination with the varicella vaccine (MMRV). Additionally, the vaccine against hepatitis A is given in a single dose at 15 months of age[3]. Despite the unquestionable benefits of vaccination, the overall adherence to vaccines is decreasing in several countries, and vaccine hesitancy has been acknowledged as a growing threat associated with the reemergence of vaccine-preventable diseases[4]. Factors such as multiparity[5], lower parental schooling[5,6], low income[7], inadequate antenatal care[6], and mothers at the extremes of age[8] have been associated with incomplete vaccination in previous studies. Additionally, vaccine immunogenicity (usually measured by its seropositivity) does not occur in 100% of vaccinees despite full vaccination. Several factors have been associated with seroconversion and seropositivity following vaccination depending on the vaccine and setting, including nutritional factors[9] and vitamin A deficiency[10]. A detailed analysis of vaccine adherence, along with the investigation of factors associated with incomplete vaccination and predictors of a positive serology following vaccination, could support the development of strategies to improve the effectiveness of vaccine programs.

In this study, we describe the occurrence of incomplete vaccination among 2-year-old children enrolled in the MINA-BRAZIL cohort, and explore factors associated with incomplete vaccination for MMR and hepatitis A vaccines. We also measure antibody responses to measles, mumps, and hepatitis, and investigate factors associated with seronegative results among vaccinated children.

MATERIALS AND METHODS

Study design and population

MINA-BRAZIL cohort is a population-based study comprising epidemiological analyses on the health and nutrition status of mothers and infants in Cruzeiro do Sul City, Acre State, located in the Northern region of Brazil. Cruzeiro do Sul City is Acre State's second largest municipality by population, with approximately 81,519 inhabitants; in 2015, 1,839 births were registered in the city, 96% of which occurred in the public maternity hospital[11].

At the cohort baseline, 1,242 pairs–mothers and their newborns with births registered between July 2015 and June 2016 and living in the urban area of the city–were considered eligible. 868 children were retained at the 2-year-old follow-up visit. Additional details on the study methods are available in previous publications of the MINA-BRAZIL Working Group[12].

For this analysis, we initially selected children retained at the 2-year-old follow-up visit, and excluded twins (due to overall higher risk of preterm birth and health complications in the first year of life; a total of 13 children), and those failing to present an official proof of vaccination (vaccination card; a total of 30 children). In total, the study population comprised 825 children. Of those, 632 underwent a blood draw at the 2-year-old follow-up visit; mumps serology was performed in all 632 blood samples, whereas 631 participants had sufficient samples for hepatitis A serology and 623 had sufficient samples for measles serology (Supplementary Figure S1).

Ethical aspects

The Ethics committees at Faculdade de Medicina and Faculdade de Saude Publica da Universidade de Sao Paulo revised and approved the study (approval Nº 3.401.859/2019 and 872.613/2014, respectively). Each participant provided written informed consent upon participation. Parents or guardians also provided written consent for the participation of minors (aged < 18 years old).

Data collection

We used standardized forms to collect sociodemographic information, housing and living conditions, clinical history, infant development, and mothers' lifestyle; anthropometric measurements were obtained by the study investigators. Data concerning antenatal care and birth were retrieved from medical charts.

Measles, mumps, and hepatitis A antibody tests

Plasma samples were frozen and shipped to a central laboratory at Faculdade de Saude Publica, Universidade de Sao Paulo, and maintained at -70 °C until analyzed. We used the following commercially available kits to measure antibody positivity: anti-measles virus ELISA IgG, Euroimmun AG for measles; Ridascreen Mumps Virus IgG, R-Biopharm (Germany) for mumps; and HAV Ab, Dia.Pro (Italy) for hepatitis A. All tests were performed according to manufacturer's instructions. For reading and interpretation of optical density, we used the Spectra Max

M5–Molecular Devices Inc. microplate with 450 nm for reading and 620 nm for reference.

Outcome variables

The primary outcome variables of the study were incomplete vaccination for MMR and hepatitis A, and seronegative results in measles, mumps and hepatitis A serology tests among the vaccinated children. Data on vaccine adherence were retrieved from official individual vaccination cards at the 2-year-old follow-up visit. Incomplete vaccination was defined as failure to receive two doses for MMR (two MMR or one MMR and one MMRV), or failure to receive a single dose of the hepatitis A vaccine, as recommended by the 2018 Brazilian vaccination calendar[13]. Seronegative results were defined for all participants with IgG levels below the cut-off levels defined for measles (200 UI/L), mumps (14 UI/mL) and hepatitis A (NC+PC/3).

Sociodemographic, antenatal care, and obstetric independent variables

We categorized the independent variables into hierarchical groups, according to a theoretical framework of factors associated with incomplete vaccination[7,14,15] and factors associated with immune response to vaccines among the pediatric population[12,16,17]. For models taking incomplete vaccination as an outcome, the distal level included: the child's gender; self-reported mother's race/skin color (registered according to the Brazilian census–white, black, mixed, native Brazilian, Asian, and categorized as white/non-white for multivariable models); mother's age at child's birth (< 19, 19–34, and ≥ 35 years old); mother's level of education (≤ 9, 10–12, and > 12 years), wealth tercile (first tercile indicates more impoverished families, and third tercile indicates wealthier families); access to Bolsa Familia allowance–public policy aimed at families in extreme poverty (yes/no); paid maternity leave (yes/no); and mother's cohabiting partner (yes/no). The intermediary level included parity (first gestation, yes/no) and preterm birth (up to 36 weeks and 6 days). The proximal level included the number of antenatal care visits (< 6 or ≥ 6 visits); type of delivery (vaginal or C-section); breastfeeding at 2 years of age (yes/no); child's previous health conditions (diarrhea; hospitalization; pneumonia; malaria; dengue); and attending childcare (yes/no). For models taking negative serology tests as outcomes, the distal level included the same variables adopted for incomplete vaccination; the intermediary level included parity, preterm birth, previous health conditions, attending childcare and number of antenatal care visits; and the proximal level included number of vaccine doses for MMR, breastfeeding at 2 years of age, child nutritional status at 2 years of age (underweight < -2 z-scores, normal -2 and +2 z-scores, and overweight > +2 z-scores; for the multivariable models, only the categories "normal" and "overweight" were included due to the low number of children in the underweight category [n = 6]), child's daily medication use (yes/no), and vitamin A deficiency (yes/no). We generated the binary variable "previous health condition", assigning "yes" for children with one or more previous health conditions, and "no" for the remaining children in the study. The child's gender was obtained as assigned at birth. The wealth index was adopted as the main indicator of the family's socioeconomic status, and it was calculated using different components and then categorized into terciles[12,18]. The first component, comprising 22.8% of the index variation, was used to calculate coefficients for each item owned by the family; for instance, a television had a 0.215 coefficient, while a refrigerator had a 0.244 coefficient.

Statistical analysis

The adherence to each vaccine and the seropositivity for mumps, measles and hepatitis A were described as counts and percentages along with 95% confidence intervals (CI). We used chi-squared tests for the unadjusted comparisons among groups defined by the independent categorical variables. We used modified Poisson regression models with robust variance, adjusted for covariates, to investigate factors associated with incomplete vaccination for MMR and hepatitis A, and to investigate factors associated with negative antibody tests for measles, mumps, and hepatitis A among the vaccinated children. The modified Poisson models were adopted to estimate the risk ratios (RR), along with 95% CI.

We selected variables for the multivariable models using a hierarchical approach with distal, intermediate, and proximal level variables as described earlier, using the theoretical structure presented by Victora *et al*.[19]. Starting from the distal level, we included in subsequent models all the variables within each level, in addition to variables from the previous model with a p-value ≤ 0.10. We used Stata (version 15.1, StataCorp, College Station, USA) in all analyses, with a significance level of 0.05.

RESULTS

825 children were included in the study, 49.7% of whom were males. The mean mother's age at birth was 25.6 years old (range 13–45). Most mothers (77.5%)

reported to have mixed skin color/race; 72.1% had more than 9 years of schooling, 77.5% reported living with a partner, and 37.2% were beneficiaries of Bolsa Familia allowance. Most (80.5%) had ≥ 6 antenatal care visits, and 58.9% reported one or more previous pregnancies. The gestational age at birth was between 37 and 42 weeks (term) for 90.6%, and 52.4% had a vaginal birth. Most children (95.2%) had a normal birth weight for gestational age.

Vaccine adherence and factors associated with incomplete vaccination for MMR and hepatitis A vaccines

Table 1 shows the frequency and percentage of complete vaccination among the study participants based on national recommendations at 2 years of age. Hepatitis A, MMRV, and MMR had the lowest percentages of vaccine compliance (74.9%, 76.7%, and 90.6%, respectively). For the remaining vaccines, the percentage of completeness was close to or above the recommended (95%)[20].

Table 1 - Frequencies and percentages of full vaccination among the children included in the study.

Vaccine	N (%)	95% CI
BCG	823 (99.8)	99.1–100.0
Hepatitis B	823 (99.8)	99.1–100.0
Rotavirus	814 (98.7)	97.6–99.3
Meningococcal C	817 (99.0)	98.1–99.6
Pneumococcal	818 (99.2)	98.3–99.7
OPV/IPV	818 (99.2)	98.3–99.7
Pentavalent	823 (96.8)	99.1–100.0
MMR	747 (90.6)	88.3–92.5
Tetraviral (MMRV)	633 (76.7)	73.7–79.6
Yellow fever	773 (93.7)	91.8–95.3
Hepatitis A	618 (74.9)	71.8–77.8

In unadjusted analyses, we found that mother's white race/skin color, paid maternity leave, multiparity, < 6 antenatal care visits, and childcare attendance were associated with incomplete vaccination for MMR. For hepatitis A, not having a cohabiting partner was associated with incomplete vaccination (Table 2).

Table 3 presents RR estimates from the final multivariable models of incomplete vaccination for MMR and hepatitis A. Only the variables retained in the final model are shown. For MMR, mother's white skin color, paid work, multiparity, less than 6 antenatal care visits and attending childcare were associated with higher risk of incomplete vaccination. For the hepatitis A vaccine, mother's white skin color and not having a cohabiting partner were associated with incomplete vaccination.

Antibody response to measles, mumps, and hepatitis A

Among the 467 children fully vaccinated for measles with available samples, seropositive results were observed in 86.9%; 3.6% had indeterminate results, and 9.4% had seronegative results. For mumps, among the 474 fully vaccinated children, 74.9% had positive antibodies, 8.0% had indeterminate results, and 17.1% had negative serologic tests. Among the participants who received a single dose of the MMR, blood samples had seropositive results for measles in 80.2%, and for mumps in 66.9%. For hepatitis A, among the 470 vaccinated children, 83.6% had seropositive results, 1.3% were indeterminate and 15.1% had a negative serology (Table 4).

The unadjusted analysis of factors associated with a negative antibody test result among the vaccinated children showed that the percentage of seronegative tests for measles were higher among children in the first wealth tercile when compared to the second and third, and among those receiving the Bolsa Familia allowance. For mumps, the children born to mothers with no paid leave, those in the second wealth tercile and those receiving the Bolsa Familia allowance had a higher percentage of seronegative tests. For hepatitis A, no variables with statistically significant associations with a seronegative result in the unadjusted analysis were found (Table 5).

Multivariable models addressing factors associated with a negative antibody test for measles, mumps, and hepatitis A

Table 6 shows the final multivariable models addressing the predictors of a negative antibody test result for measles, mumps, and hepatitis A. Among the children vaccinated with at least one dose of MMR and tested for measles serology, we found that participants receiving the Bolsa Familia allowance had a 1.70 times higher risk of having a seronegative result (95% CI 1.14–2.55) when compared to the participants who did not receive the allowance; those who had received two vaccine doses had a 36% lower risk of a seronegative measles result when compared to the participants vaccinated with a single shot (95% CI 0.41–1.00). Receiving the Bolsa Familia allowance was also significantly associated with increased risk of a seronegative result for mumps (adjusted RR = 1.35, 95% CI 1.01–1.81). Interestingly, deficient levels of vitamin A were associated with higher risk of a negative antibody result for mumps (adjusted RR = 1.35, 95% CI 1.01–1.81). As for hepatitis A, we failed to find factors with statistically significant associations with a negative antibody test result in the final multivariable model.

Table 2 - Unadjusted associations between the independent variables and adherence to vaccination for MMR and hepatitis A.

	Total	MMR % (95% CI)	p-value	Hepatitis A% (95% CI)	p-value
Distal variables					
Child gender					
Male	410	72.9 (68.4–77.2)	0.086	74.6 (70.1–78.8)	0.856
Female	415	78.1 (73.8–82.0)		75.2 (70.7–79.3)	
Mother's skin color					
White	108	63.9 (54.1–72.9)	**0.002**	68.5 (58.9–77.1)	0.079
Non-white	702	77.6 (74.4–80.7)		76.4 (73.0–79.5)	
Paid maternity leave					
Yes	385	72.0 (67.2–76.4)	**0.023**	74.6 (69.9–78.8)	0.792
No	438	78.8 (74.6–82.5)		75.3 (71.0–79.3)	
Wealth index					
First tercile	274	76.6 (71.2–81.5)	0.571	73.4 (67.7–78.5)	0.742
Second tercile	277	73.3 (67.7–78.4)		76.2 (70.7–81.0)	
Third tercile	274	76.6 (71.2–81.5)		75.2 (69.6–80.2)	
Mother's schooling					
≤ 9 years	226	78.3 (72.4–83.5)	0.457	78.3 (72.4–83.5)	0.329
10–12 years	422	75.6 (71.2–79.6)		73.2 (68.7–77.4)	
>12 years	162	72.8 (65.3–79.5)		76.5 (69.3–82.8)	
Mother's age at childbirth					
< 19 years	123	82.1 (74.2–88.4)	0.138	69.9 (61.0–77.9)	0.189
19–35 years	613	73.9 (70.2–77.3)		75.0 (71.4–78.4)	
≥ 35 years	89	77.5 (67.5–85.7)		80.9 (71.2–88.5)	
Has a cohabiting partner			0.689		
Yes	628	75.5 (71.9–78.8)		77.6 (74.1–80.8)	**0.006**
No	182	76.9 (70.1–82.8)		67.6 (60.3–74.3)	
Has access to Bolsa Familia allowance			0.978		0.575
Yes	301	75.7 (70.5–80.5)		76.4 (71.2–81.1)	
No	509	75.8 (71.9–79.5)		74.7 (70.6–78.4)	
Intermediate variables					
First pregnancy					
Yes	333	82.0 (77.4–86.0)	**0.001**	77.2 (72.3–81.6)	0.303
No	477	71.5 (67.2–75.5)		74.0 (69.8–77.9)	
Preterm birth					
Yes	68	79.4 (67.9–88.3)	0.435	76.5 (64.6–85.9)	0.757
No	757	75.2 (71.9–78.2)		74.8 (71.5–77.8)	
Proximal variables					
Previous health condition					
Yes	364	75.6 (70.8–79.9)	0.970	73.9 (69.1–78.3)	0.565
No	460	75.4 (71.2–79.3)		75.7 (71.5–79.5)	
Type of delivery					
Vaginal	432	74.5 (70.2–78.6)	0.493	73.2 (68.7–77.3)	0.221
C-section	393	76.6 (72.1–80.7)		76.8 (72.4–80.9)	
Breastfeeding at 2 years of age			0.769		0.130
Yes	287	74.9 (69.5–79.8)		71.8 (66.2–76.9)	
No	538	75.8 (72.0–79.4)		76.6 (72.8–80.1)	
Antenatal care visits					
< 6	160	63.1 (55.2–70.6)	**< 0.001**	70.0 (62.3–77.0)	0.095
≥ 6	660	78.8 (75.5–81.9)		76.4 (72.9–79.6)	
Attending childcare					
Yes	20	50.0 (27.2–72.8)	**0.007**	70.0 (45.7–88.1)	0.608
No	805	76.2 (73.1–79.1)		75.03 (71.9–78.0)	

MMR = mumps, measles, and rubella; First tercile of wealth index indicates poorer families; Third tercile indicates wealthier families

Table 3 - Multivariable models addressing the predictors of incomplete vaccination for MMR and hepatitis A.

	MMR aRR	95% CI	p-value	Hepatitis A aRR	95% CI	p-value
Child gender			0.080			
Female	Reference (1.00)			-	-	-
Male	1.24	0.97–1.58				
Mother's skin color			**0.005**			**0.027**
White	Reference (1.00)			Reference (1.00)		
Mixed ethnicity	0.66	0.50–0.87		0.71	0.52–0.96	
Paid leave			**0.016**			
No	Reference (1.00)	1.06–1.72		-	-	-
Yes	1.35					
First pregnancy			**< 0.001**			
No	Reference (1.00)			-	-	-
Yes	0.61	0.47–0.80				
Has a cohabiting partner	-	-				**0.002**
No			-	Reference (1.00)		
Yes				0.67	0.52–0.87	
Breastfeeding at 2 years old						0.067
No	-	-	-	Reference (1.00)		
Yes				1.25	0.98–1.60	
Number of antenatal care visits			**< 0.001**	-	-	-
< 6	Reference (1.00)	-				
≥ 6	0.61	0.47–0.78				
Attending childcare			**0.007**	-	-	
No	Reference (1.00)					-
Yes	1.87	1.19–2.96				

Table 4 - Frequencies, percentages, and 95% confidence intervals of seropositive results for measles, mumps, and hepatitis A among the study participants, according to vaccination status.

Vaccination status	Seropositive test N (%)	95% CI	Seronegative test N (%)	95% CI	Undetermined N (%)	95% CI
Measles						
2 doses (n = 467)	406 (86.9)	83.5–89.8	44 (9.4)	6.9–12.4	17 (3.6)	2.1–5.7
1 dose (n = 101)	81 (80.2)	71.1–87.5	17 (16.8)	10.1–25.5	3 (2.9)	0.6–8.4
Unvaccinated (n =55)	3 (5.4)	1.1–15.1	51 (92.7)	82.4–97.9	1 (1.8)	0.0–9.7
Mumps						
2 doses (n = 474)	355 (74.9)	70.7–78.7	81 (17.1)	13.8–20.7	38 (8.0)	5.7–10.8
1 dose (n = 103)	69 (66.9)	57.0–75.9	29 (28.2)	19.7–37.8	5 (4.8)	1.5–10.9
Unvaccinated (n = 55)	12 (21.8)	11.8–35.0	41 (74.5)	61.0–85.3	2 (3.6)	0.4–12.5
Hepatitis A						
Vaccinated (n = 470)	393 (83.6)	79.9–86.8	71 (15.1)	11.9–18.6	6 (1.3)	0.4–2.8
Unvaccinated (n = 161)	39 (24.2)	17.8–31.5	122 (75.7)	68.4–82.1	0	-

DISCUSSION

In this population-based cohort study, we described the frequency and percentage of participants with full vaccination in line with the national vaccination calendar, as well as the factors associated with incomplete vaccination for MMR and hepatitis A. We also presented data on antibody tests for measles, mumps, and hepatitis A in the study population, and investigated the factors associated with seronegative results among vaccinees.

Our findings demonstrate that MMR, MMRV, and hepatitis A vaccines failed to reach the recommended coverage of 95%[20] in the study population, and support national reports that show declining trends of vaccine adherence in Brazil since 2016[20,21]. The reduction of vaccine compliance is concerning, as it has been associated

Table 5 - Unadjusted associations between the independent variables and seropositive results for measles, mumps, and hepatitis A.

	Total N = 568	Measles seropositive test %	p-value	Total N = 577	Mumps seropositive test %	p-value	Total N = 470	Hepatitis A seropositive test %	p-value
Distal variables									
Child gender									
Male	281	82.9	0.057	285	71.2	0.225	234	81.6	0.245
Female	287	88.5		292	75.7		236	85.6	
Mother's skin color									
White	70	87.1	0.715	72	68.1	0.283	58	84.5	0.820
Mixed ethnicity	490	85.5		497	74.0		407	83.3	
Paid leave									
Yes	245	86.9	0.458	252	77.8	**0.036**	207	81.2	0.208
No	321	84.7		323	69.9		262	85.5	
Mother's age									
<1 9 years	93	87.1	0.398	94	69.1	0.175	69	85.5	0.412
19–34 years	409	86.3		416	73.1		346	82.4	
≥ 35 years	66	80.3		67	82.1		55	89.1	
Wealth index									
First tercile	187	80.2	**0.026**	187	75.4	**0.027**	155	83.9	0.815
Second tercile	199	89.4		203	67.0		164	84.8	
Third tercile	182	87.3		187	78.6		151	82.1	
Mother's schooling									
≤ 9 years	155	84.5	0.080	156	70.5	0.324	136	84.6	0.648
10–12 years	298	83.9		301	72.8		238	84.0	
> 12 years	107	92.5		112	78.6		91	80.2	
Has a cohabiting partner									
Yes									
No	437	85.6	0.868	443	73.8	0.593	372	82.5	0.289
	123	86.2		126	71.4		93	87.1	
Has access to Bolsa Familia allowance			**0.011**			**0.022**			0.464
Yes	215	80.9		218	67.9		182	81.9	
No	345	88.7		351	76.6		283	84.4	
Intermediate variables									
Previous health condition									
Yes									
No	258	85.3	0.783	262	71.4	0.266	209	82.8	0.672
	309	86.1		314	75.5		260	84.2	
Attending childcare									
Yes	13	100.0	0.137	14	71.4	0.860	12	75.0	0.414
No	555	85.4		563	73.5		458	83.8	
Number of antenatal care visits									
< 6	94	85.1	0.823	97	71.1	0.559	83	78.3	0.153
≥ 6	471	85.9		477	74.0		386	84.7	
Preterm birth									
Yes	46	86.9	0.805	48	83.3	0.106	39	92.3	0.126
No	522	85.6		529	72.6		431	82.8	
First pregnancy									
Yes	250	86.0	0.862	254	72.8	0.827	205	80.9	0.204
No	310	85.5		315	73.6		260	85.4	
Proximal variables									
Number of MMR doses									
1 dose	101	80.2	0.079	103	66.9	0.100	–	–	–
2 doses	467	86.9		474	74.9				

Table 5 - Unadjusted associations between the independent variables and seropositive results for measles, mumps, and hepatitis A. (cont.)

	Total N = 568	Measles seropositive test %	p-value	Total N = 577	Mumps seropositive test %	p-value	Total N = 470	Hepatitis A seropositive test %	p-value
Breastfeeding at 2 years of age									
Yes	195	87.2	0.478	198	71.2	0.372	152	85.5	0.439
No	373	84.9		379	74.7		318	82.7	
Nutritional status at 2 years of age									
Underweight	1	100.0	0.830	1	0.0	0.135	1	100.0	0.796
Normal	524	85.9		533	73.2		433	83.8	
Overweight	42	83.3		42	80.9		36	80.6	
Daily medications									
Yes	42	90.5	0.362	42	71.4	0.754	35	85.7	0.727
No	526	85.4		535	73.6		435	83.4	
Vitamin A									
Not deficient	408	85.1	0.253	417	75.8	**0.018**	328	83.8	0.585
Deficient	136	89.0		136	65.4		120	81.7	

Table 6 - Multivariable models addressing the predictors of a negative antibody test result for measles, mumps, and hepatitis A.

Measles	Adjusted RR	95% CI	p-value
Has access to Bolsa Familia allowance			
No	Reference (1.00)		
Yes	1.70	1.14–2.55	**0.010**
Received 2 vaccine doses			
No	Reference (1.00)		
Yes	0.64	0.41–1.00	**0.048**
Mumps	**Adjusted RR**	**95% CI**	**p-value**
Maternal paid work			
No	Reference (1.00)		
Yes	0.76	0.56–1.02	0.071
Wealth index			
First tercile	Reference (1.00)		
Second tercile	1.41	1.02–1.95	**0.037**
Third tercile	1.13	0.75–1.71	0.555
Has access to Bolsa Familia allowance			
No	Reference (1.00)		
Yes	1.35	1.01–1.81	**0.045**
Received 2 vaccine doses			
No	Reference (1.00)		
Yes	0.74	0.54–1.03	0.072
Vitamin A			
Not deficient	Reference (1.00)		
Deficient	1.39	1.05–1.85	**0.023**

RR = risk ratio; CI = confidence interval

with the resurgence of preventable diseases, both among unvaccinated and vaccinated groups, as observed recently with measles and mumps outbreaks[22].

We identified that mother's white skin color, paid maternity paid, multiparity, lower number of antenatal care consultations and attending childcare were associated with incomplete MMR vaccination, whereas mother's white skin color and not having a cohabiting partner were associated

with incomplete vaccination for hepatitis A. These findings suggest a strong influence of social determinants on vaccine compliance and indicate specific subgroups for whom vaccination campaigns and targeted strategies should be prioritized.

Although prior studies suggest that mother's white skin color is associated with higher probability of offspring vaccination[14,23], our findings demonstrate a negative association between this characteristic and vaccine compliance. One possible explanation is the stronger vaccine hesitancy among more affluent families and families with white skin in Brazil, as suggested previously[24]. In a recent study conducted in the Southern region of Brazil, multiparity, lower number of antenatal care visits, breastfeeding at 12 months of age, and higher family incomes were associated with incomplete vaccination[5]. Other studies have also shown an association between multiparity and lower vaccine adherence[6,25-27]. This finding could be related to social conditions, since economically vulnerable families tend to be larger; it could also reflect the fact that caregivers and guardians overseeing a larger number of children may find more barriers in accessing healthcare services[5]. Paid maternity leave, not having a cohabiting partner, and attending childcare were factors associated with incomplete vaccination in our study; these findings could be related to difficulties in accessing healthcare services, which mostly operate during business hours only–a barrier for mothers who are in the workforce and do not have a partner to share parenting duties.

Children whose mothers had fewer than 6 antenatal care visits during pregnancy, the minimal number recommended by the Ministry of Health[28], had a higher risk of incomplete vaccination. These data are in accordance with results from a previous study from the Maranhao State[14], and suggest that pregnant women who follow the antenatal care guidelines also have better adherence to childcare recommendations, and are likely to have a stronger retention in the healthcare service. Finally, although prior studies suggested an association between higher socioeconomic status and incomplete vaccination in children[27], we failed to find this relationship. Since our study exclusively recruited exclusively children born in the public maternity hospital, it is possible that our population had a smaller income variability, precluding the identification of this association.

Our results show that antibody positivity for hepatitis A was 83.6% among the vaccinees, in accordance with existing data showing seropositivity of 80–100% following vaccination with a single dose in healthy individuals[29]. Despite the high percentage of seropositivity, some studies suggest that the duration of positive antibodies after a single dose of hepatitis A vaccine may be shorter than that observed after a two-dose regimen[31-33]. We found no statistically significant associations between independent variables and seropositivity for hepatitis A in our study.

In the analysis of factors associated with seropositivity for measles and mumps, we found a higher percentage of children with positive antibodies among those receiving two MMR doses (or one MMR and one MMRV) when compared to those receiving a single dose. This finding supports the current recommendations from the PNI. In the multivariable models, the children whose families received the Bolsa Familia allowance had a higher risk of seronegative tests for both measles and mumps. The Bolsa Familia allowance is a public policy aimed at supporting citizens in extreme poverty, reducing social inequalities throughout the country[34]. Although there is no direct link between the program and antibody responses following vaccination, we hypothesize that the association results from environmental and nutritional factors that were not completely adjusted for, despite the use of multivariable models with hierarchical categorization of independent variables. Children in families receiving the Bolsa Familia allowance are more likely to face dietary issues and other external factors that may influence vaccine responses, as seen for measles[9], poliomyelitis[33], and pertussis[34].

We also found a statistically significant association between vitamin A deficiency and negative antibodies for mumps among the vaccinated children of the multivariable model. Vitamin A deficiency affects children and adults across the globe; according to WHO, nearly 190 million pre-school children have vitamin A deficiency[35]. Previous studies reported that vitamin A deficiency can be associated with a higher risk of infectious diseases, including respiratory and gastrointestinal infections[10]. Furthermore, vitamin A deficiency has been associated with vaccine responses[10,36,37]. Patel *et al*.[36] conducted a randomized trial showing that vitamin A supplementation can improve influenza vaccine responses among children with insufficient blood levels; similarly, Penkert *et al*.[10] published a study showing that vitamin A deficiency and supplementation can affect immune responses to infectious diseases and vaccine immunogenicity. Understanding the influence of vitamin A levels and supplementation on immune responses to vaccines could support the development of strategies to improve the effectiveness of vaccine programs.

Limitations of the study

Our study had a few limitations. Approximately 30% of participants initially enrolled in the MINA-BRAZIL cohort were lost after the follow-up at the 2-year-old visit. However, it is unlikely that this implies a substantial risk of retention

bias, since the baseline cohort and those retained at the 2-year-old visit had no significant differences concerning sociodemographic characteristics (mother's schooling; percentage of primiparous mothers; type of delivery; child gender; percentage of preterm births; and percentage of children with low birth weight)[12]. We obtained vaccine adherence information from the official vaccination cards only, not exploring other sources such as medical charts or the PNI information systems. We have no information on antibody responses before the vaccination, and did not obtain systematic register of measles, mumps, and hepatitis A occurrence among the study participants. Alternative multivariable models for binary outcomes could have been used, although modified Poisson's models are usually well accepted for generating estimates of risk ratios[38]. Finally, we categorized the independent variables into hierarchical groups and selected the variables for multivariable models using a mathematical threshold; other strategies could have been adopted, potentially impacting the final results.

CONCLUSION

Despite these limitations, our study brings important contributions. We showed that the adherence to MMR and hepatitis A vaccines was below the national recommendations among the study population. We also demonstrated that social factors are associated with both vaccine compliance and antibody positivity, and vitamin A deficiency can impact on mumps vaccine response. Strategies to improve vaccine adherence and mitigate social and nutritional factors associated with reduced immune responses following vaccination should be developed and implemented, including targeted campaigns, public policies to reduce poverty, and the supplementation of vitamin A and other nutrients for children with deficient levels.

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