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Factors associated with protective antibody levels to vaccine preventable diseases in internationally adopted children[☆]

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Abstract

To determine which factors are predictive of protective antibody against vaccine-preventable diseases in internationally adopted children, we evaluated 562 children with serologic testing for at least one vaccine antigen before receiving a US vaccination. Vaccination status was defined as the number-of-doses recorded and as the presence of an up-to-date and valid record according to the American Academy of Pediatrics and the Advisory Committee on Immunization Practices guidelines. The number-of-doses recorded was the best predictor of protective antibody. These findings suggest that other options for immunization verification guidelines for internationally adopted children should be considered by policy makers.

Keywords

International adoption; Immunization; Serology; Vaccine preventable diseases

1. Introduction

Over the past decade, nearly 200,000 children were adopted internationally by US families [1]. As part of a comprehensive health visit shortly after arrival, the American Academy of Pediatrics (AAP) recommends that the vaccine records of internationally adopted children be examined for completeness to determine which immunizations are needed [2]. The AAP

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2010.09.098.

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[2], the Advisory Committee on Immunization Practices (ACIP) [3], and the Infectious Disease Society of America [4] advise that written records may be considered valid if: the vaccines, dates of administration, numbers of doses, intervals between doses, and patient's age at the time of immunization are all consistent with the current US or World Health Organization schedule. The guidelines state that if there are any concerns about the records, re-immunization or serologic testing is recommended for those vaccine antigens in question. Verification of the immunization records of adoptees is challenging since immunization schedules and vaccines vary by birth country, thus, leaving health care providers to frequently re-immunize or do serologic testing for internationally adopted children. In addition to the uncertainty of interpreting the validity of the immunization records, it is unclear whether other factors such as birth country, gender, age, history of institutionalization, nutritional status, or a history of disease play a role in determining whether a child has adequate immunity against a given vaccine preventable disease.

While several studies have examined whether internationally adopted children have documentation of immunizations [5-8] and protective antibody levels to vaccine preventable diseases [9-19], only two studies have comprehensively examined factors associated with protection through multivariable analyses [15,16]. The results of these studies varied and the reasons for these differences are not entirely clear. Given the lack of consistent conclusions in previous studies and to provide data for evidenced-based guidelines, we examined the immunization records of internationally adopted children using two methods to define vaccination status. Our objective was to determine which definition of vaccination status would be most predictive of protective antibody against diphtheria, tetanus, polio, hepatitis B, measles, mumps, rubella and varicella vaccine antigens, while controlling for other factors in a multivariable model.

2. Methods

2.1. Study population

Children evaluated at the International Adoption Center at Cincinnati Children's Hospital Medical Center (CCHMC) from November 1999 through June 2004 were included in the study if adopted from: Russia, China, Guatemala, Kazakhstan, or South Korea and had a serologic test within 6 months of arrival for at least one vaccine antigen for which they had not received a US vaccine dose prior to testing. These countries represented the five countries with the largest number of children in our clinic population. For the US, these same five countries also had the largest number of internationally adopted children during the study period. In addition, the distribution of the top five countries in our study was the same distribution for all children evaluated at our Center regardless if they were in the study. Serologic testing included diphtheria, tetanus, polio, and hepatitis B virus (HBV) for children ≥ 5 months old and measles, mumps, rubella, and varicella if they were ≥ 12 months old. Demographic and clinical information was collected on all children including the child's birth country, gender, birth date, initial visit date, institutionalization history (< 6 months was considered non-institutionalized), weight at initial visit, documentation of immunization record (any written documentation), dates of vaccinations, history of disease (for measles, mumps, rubella, and varicella), and serology dates and results. The CCHMC Institutional Review Board approved the study.

2.2. Evaluation of immunization records

Families were encouraged to provide documentation of their child's birth country immunization record to the clinic visit. Any written record for any vaccine was accepted as documentation. From this documentation, each vaccination was examined to determine if it was valid according to 2006 AAP [20] and ACIP [3] standard, recommended, and

accelerated schedules, with respect to the age received and interval between doses (Appendix A). Recorded vaccinations were considered *invalid* if the date of administration was absent, preceded the child's birth date, or did not exist (e.g. 31st day of a 30-day month). For diphtheria and tetanus, if the vaccine product (e.g. Td) was inappropriate for the child's age, the dose was considered invalid. The oral polio (OPV) schedule was used, as most adoptees received OPV.

2.3. Methods to define vaccination status

For each vaccine antigen, two variables were generated to define a child's vaccination status. The first definition, number-of-doses recorded (ND-R), was the least restrictive. ND-R was an ordinal variable representing the number of recorded vaccinations a child received in his/her birth country regardless of whether they were valid. The second definition, up-to-date and valid (UTD-V), used the AAP and ACIP recommended approach for evaluating vaccination records [2,3]. UTD-V was a dichotomous variable where a child's record was considered up-to-date and valid if the number of valid doses was greater than or equal to the number of required doses for the child's age.

2.4. Laboratory testing

Standard serologic assays and methods at commercial laboratories were used. More than 95% of children had testing for a given vaccine antigen at the same laboratory utilized by CCHMC during the study period. For diphtheria and tetanus, immunoglobulin G (IgG) enzyme-linked immunosorbent assays (ELISA) with a definition of protective antibody for diphtheria > 0.10 IU/mL [21-24] and for tetanus > 0.10 IU/mL [21,24-26]. For polio, neutralizing antibody to each polio serotype was performed and the definition of protection was a titer of $\geq 1:8$ for each serotype [21,27,28]. An ELISA for HBV (hepatitis B surface antibody/anti-HBs) was used and the definition of protection was ≥ 10 mIU/mL [21,29,30]; the Abbott assay (Chicago, IL) [30] was used in $> 95\%$ of children. For measles and mumps, immunofluorescent antibody assays were used for 97% of children with cut-off values of $\geq 1:8$ for measles [31,32] and $\geq 1:16$ for mumps [32,33]; the remaining children had immunosorbent assays done. For rubella, all children had immunosorbent assays done [34]; 95% of the assays had an ELISA done with a cut-off value of ≥ 10 IU/mL as positive [35]. For varicella, 97% of children had an ELISA done with a qualitative cut-off as positive with an OD ratio of ≥ 1.10 (Zeus Scientific, Inc. Rarita, NJ) [34,36].

2.5. Statistical analysis

Variables were descriptively summarized as medians and ranges for non-normally distributed variables and as percentages for categorical variables. For our primary outcome of interest, a dichotomous variable was generated as a surrogate for immunity and was based on the defined protective level of antibody for each vaccine antigen [21]. The dichotomous variable was defined as having a "protective level" if the numeric value of the lab result was above the standard which was considered protective. Values below the standard were designated as having a "non-protective level."

For each vaccine antigen, univariate logistic regression analyses were performed for the following variables: birth country, gender, age, non-institutionalization, adequate nourishment, documented immunization record, vaccination status, and history of disease (for varicella). Guatemala was used as the reference group for birth country given that its sample size was large enough to allow multivariable analysis, gender distribution was similar to the other countries (except China), and they had high levels of protection. Each child's weight at the initial evaluation was converted to weight-for-age z-scores using CDC growth charts [37]. A weight-for-age z-score two or more SDs below the mean was used as a

surrogate for malnutrition [38]. Values above this cutoff were defined as “adequately nourished.”

For ND-R, the reference group was zero doses. Variables with p -values ≤ 0.20 in the univariate analyses were included in the multivariable analyses. Multicollinearity among the variables was examined and the two variables used to define vaccination status were correlated. Therefore, two multivariable models were fit for each vaccine antigen, one for each of the variables used to define vaccination status: ND-R and UTD-V. The model with the lowest Akaike’s Information Criterion (AIC) was considered optimal for predicting immunity; models with an AIC difference of < 2 were considered comparable [39]. All tests were two-sided and p -values ≤ 0.05 or 95% confidence intervals (CI) for the odds ratio that did not include the value of one were considered statistically significant. The significance level was not adjusted for multiple comparisons. Statistical analyses were performed with SAS® version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Study population characteristics are provided in Table 1. The study included 562 children; 42% were from Russia. Overall, 55% were female; however, 91% of Chinese children were female. South Korean and Guatemalan children were younger (all p -values < 0.006) and more likely to have been non-institutionalized (all p -values < 0.001) than children from other countries. Most children (93%) had documentation of at least one vaccination in their birth country and there were no differences among birth country.

3.2. Reasons for invalid vaccine records

Reasons for invalid immunizations by vaccine antigen are shown in Table 2. Overall, the proportion of children without an UTD-V record was highest for varicella (52%) and lowest for measles (18%). The most common reason that a child’s record was not UTD-V was due to not having enough doses of vaccine, followed by receipt of vaccine prior to the recommended age, and lastly an insufficient interval between doses. Children with incorrect vaccine dates represented a very small proportion (2–3%).

3.3. Proportion of children with protective antibody

The proportion of children with protective antibody by vaccine antigen and birth country is shown in Tables 3a and 3b. For diphtheria, tetanus, polio, and HBV, the overall proportion of children with protection was similar for children who had ≥ 3 recorded doses using the ND-R and UTD-V methods (Table 3a). In contrast, for measles, mumps, rubella, and varicella, the overall proportion of children with protective antibody was higher using the ND-R method compared to the UTD-V method (Table 3b). This difference was probably because children without any doses were considered up-to-date for measles, mumps, and rubella until they were 16 months old and for varicella, until 19 months of age.

3.4. Univariate analyses

Univariate analyses were done to examine factors associated with immunity for each vaccine antigen (Tables 4a and 4b). Both the ND-R and UTD-V methods were significantly associated with protection for diphtheria, tetanus, polio, and HBV (Table 4a). For diphtheria and tetanus, protective levels of antibody were also associated with birth country, non-institutionalization, adequate nourishment, and having an immunization record. For polio, increasing age and adequate nourishment were associated with immunity. For HBV, non-institutionalization and having an immunization record were associated with immunity, while increasing age was inversely associated with immunity.

For measles, increasing age and ND-R were significantly associated with immunity, while for mumps, birth country, increasing age, adequate nourishment, and ND-R were significantly associated with protection (Table 4b). For rubella, all factors except having an immunization record were significantly associated with immunity.

For varicella, birth country, increasing age, and varicella disease history were significantly associated with protection. However, UTD-V was inversely associated with immunity. This was likely due to the fact that very few children received the varicella vaccine yet all children < 19 months of age were considered to be up-to-date for varicella. Despite their up-to-date status, these children were less likely to have a history of varicella compared to children ≥19 months of age, and thus less likely to be protected. This caused a significant, inverse association between being up-to-date and being protected.

3.5. Multivariable analyses by vaccine antigen

For each vaccine antigen, two separate multivariable statistical models were generated. Each model included one of the variables used to define vaccination status along with the covariates with $p \leq 0.20$ in the univariate analyses. For most antigens, the ND-R model was considered the optimal model because it had a lower AIC compared to the UTD-V model. Table 5a displays the results for diphtheria, tetanus, polio, and hepatitis B. Table 5b displays the results for measles, mumps, rubella, and varicella.

3.5.1. Diphtheria—Vaccination status in the ND-R model was significantly associated with protective antibody but was not significant in the UTD-V model. Chinese children were less likely to be immune compared to Guatemalan children. Having an immunization record was also associated with protection in the UTD-V model. The ND-R model was the better model for assessing factors associated with diphtheria immunity. For the ND-R model, children with 3 recorded doses were more likely to be protected compared to children with zero recorded doses (adjusted OR = 5.88).

3.5.2. Tetanus—For both models, vaccination status was significantly associated with protective antibody levels and Chinese children were less likely to be immune compared to Guatemalan children. For the UTD-V model, being adequately nourished and having an immunization record was associated with protection. The ND-R model was the better model for assessing factors associated with tetanus immunity finding children with 3 doses more likely to have protective antibody compared to those with zero doses (adjusted OR = 11.63).

3.5.3. Polio—Increasing age, non-institutionalization, and vaccination status were associated with immunity in both models. For the UTD-V model, Kazakhstani children were more likely to be protected compared to Guatemalan children (adjusted OR = 6.64). Overall, the UTD-V model and the ND-R model were comparable for assessing factors associated with polio protection; children with an UTD-V record were more likely to be protected (adjusted OR = 2.70), and children with 3 recorded doses were more likely to have protective antibody compared to those with zero doses (adjusted OR = 3.44).

3.5.4. Hepatitis B virus—For both models, vaccination status was the only factor associated with immunity. The ND-R model was the better model for assessing factors associated with HBV protection; children with ≥ 3 doses were more likely to be immune compared to children with zero doses (adjusted OR = 8.91).

3.5.5. Measles—Vaccination status was significantly associated with immunity in the ND-R model and increasing age was significantly associated with protection for both models. In the UTD-V model, being from Russia was associated with a lack of protective antibody. The

ND-R model was the better model for assessing factors associated with measles protection. In this model, children with ≥ 1 dose were more likely to have protective antibody compared to children with zero doses (adjusted OR = 14.20) and increasing age was also significantly associated with immunity.

3.5.6. Mumps—For both models, increasing age was significantly associated with protection, while being from Russia and China were significantly associated with a lack of protection. The ND-R model was the better model for assessing factors associated with mumps immunity. In the ND-R model, children with ≥ 1 dose were more likely to be immune compared to children with zero doses (adjusted OR = 3.98).

3.5.7. Rubella—In both models, vaccination status and increasing age were significantly associated with protective antibody. Being from China or Kazakhstan was significantly associated with lack of immunity in both models, while being from Russia was associated with a lack of protection for the UTD-V model. The ND-R model was the better model for assessing factors associated with rubella immunity. In this model, children with ≥ 1 dose were more likely to be immune compared to children with zero doses (adjusted OR = 20.98).

3.5.8. Varicella—Our analysis included varicella since international adoptees are assessed for this vaccine preventable disease and there is concern that vaccine storage issues may decrease the immunogenicity of the vaccine. Even though there was low varicella vaccine use in the birth countries and years studied, we were interested in examining the association between history of varicella disease and immunity. In the multivariable analyses, when age and history of disease were included, the number of doses was no longer associated with protection in the ND-R model. Also, an inverse association between protection and UTD-V was observed. A possible explanation for this anomaly is that children < 19 months of age were considered to be up-to-date for varicella, based on age alone. Children ≥ 19 months needed to have at least one dose to be considered up-to-date. Because only 7% of the children had received varicella vaccine, the up-to-date status was primarily a surrogate for age. Yet, as age increased, children were also more likely to have a history of disease. Therefore, children ≥ 19 months were more likely to have protective antibody (due to wild type disease), but less likely to be up-to-date (have receipt of vaccine). For both models, increasing age and history of disease were significant with similar adjusted odds ratios. Children with a history of varicella were more likely to have protection compared to those without (adjusted OR = 19.3).

4. Discussion

Our study examined factors associated with protective antibody against vaccine preventable diseases in a large cohort of internationally adopted children, focusing on the five countries from which the most children emigrated during the years of this study. In the univariate analyses, country specific differences were detected and varied by vaccine antigen. Similar to our findings, other studies have reported lower levels of protection in Chinese children [11,15-17]. However, the results of previous studies compared to our study varied with respect to age [10,13,15,17], institutionalization [9,10,15,16], and nutritional status [10,13,15,16]. Given these differences, we felt it was important to adjust for these factors in multivariable analyses.

In our study, 93% had documentation of receiving at least one vaccine in their birth country compared to other studies where documentation varied greatly from 35 to 85% [5-8]. Our high proportion of children with an immunization record may have been due to our emphasis on bringing vaccination records to the clinic appointment, improved vaccine coverage, and/or improvements in immunization documentation in the child's birth country.

Interestingly, we found very few errors in the vaccination records as discussed in other studies [9,11,13]. Instead, the major reason for a lack of UTD-V status in our study was not receiving enough doses and not due to incorrect dates.

To our knowledge, this is the first study to examine different methods for assessing the immunization records of internationally adopted children with regard to protective antibody levels. The two methods yielded fairly similar results for diphtheria, tetanus, polio, and HBV. However, for measles, mumps, and rubella, children with ≥ 1 recorded dose (ND-R) were more likely to be protected than children who were UTD-V. This could be due to the fact that measles immunization is often given prior to 1 year of age in areas in which measles is endemic.

Our study adjusted for several factors in the multivariable analyses to determine which factors were associated with immunity. Compared to Guatemalan children, we found Chinese children had decreased protection for diphtheria, tetanus, mumps, and rubella, while Russian children had decreased immunity for mumps and Kazakhstani children were less likely to be immune to rubella. The only other factors besides vaccination status that were significantly associated with protection were increasing age for polio, measles, mumps, and rubella, and non-institutionalization for polio. For varicella, since so few children were vaccinated, increasing age and history of disease were the most important predictors. For all antigens except polio and varicella, the optimal model for predicting protection was the least restrictive model where vaccination status was defined as the ND-R.

Only two previous studies used multivariable analyses to evaluate protection using immunization records in internationally adopted children [15,16]. In the *Verla-Tebit* study, Chinese children were more likely to be unprotected against tetanus, polio serotype 1 and HBV compared to Russian children [16]. *Cilleruelo* used “record with updated number of doses for age,” similar to UTD-V (except that doses were not excluded for being administered too young or within an insufficient interval between doses), and found a significant association with protection against measles, mumps, rubella, and HBV, but not diphtheria, tetanus, or polio [15]. In our study, UTD-V was significant for all antigens except for diphtheria, measles and mumps. Differences between our results and *Cilleruelo*’s for tetanus and polio may exist because children (especially younger children) may still have had protection from prior vaccinations and age cutoffs for defining up-to-date were different. In our analysis, children with an adequate number of prior doses who had reached the *minimum* recommended age for a subsequent vaccination were considered UTD-V until they *exceeded* the *maximum* recommended age, whereas *Cilleruelo* used a younger age cutoff [15]. In *Cilleruelo*’s study, it is possible that younger children defined as not up-to-date were still protected by prior doses, which would explain the lack of association.

While there are several strengths to our study including a large sample size and ability to use multivariable analyses to examine factors associated with protection, there are limitations to our study. We were only able to include the five countries from which most children immigrated to the US. Therefore, our conclusions may be different for other countries. In order to perform statistical comparisons, we wanted to use a country that had high levels of overall protection as our reference group. Both Guatemala and South Korea met this specification. Because the number of children from Guatemala was larger than the number from South Korea, we decided to use Guatemala as our reference group. Children from Guatemala do have some demographic differences – notably that they are often not institutionalized (as they live in private families/foster care) and are younger. In addition, the time period of the study may not be generalizable to the current time as the quality of vaccines and vaccine uptake may have changed over time. In addition, there have been changes in the demographics of international adoptees with an increase in the prevalence of

Ethiopian adoptions. It will be important to examine whether similar results will be seen in children from Ethiopia. Similar to other studies, we were unable to determine if the presence of protective antibody was due to immunization, wild-type disease in the community (polio, measles, mumps, rubella, and varicella), vaccine-associated varicella or polio virus, or waning maternal antibody. However, we do not feel this is a major limitation given the strength of the association with protection seen with the increased number of immunization doses recorded.

5. Conclusion

Our results provide data for evidence-based guidelines for immunization recommendations for internationally adopted children. The two methods used to assess immunization records of internationally adopted children were fairly comparable, however for most vaccine antigens, the model using the number-of-doses recorded was the better predictor of protective antibody. For clinicians evaluating the birth country immunization record, using the ND-R method may be simpler and a more straightforward method than determining whether or not a child is up-to-date for age (UTD-V). Policy makers should consider expanding the options available for evaluating immunization records in internationally adopted children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
CCHMC	Cincinnati Children's Hospital Medical Center
CI	95% confidence interval
DTP	diphtheria tetanus pertussis
ELISA	enzyme-linked immunosorbent assay
HBV	hepatitis B virus
MMR	measles mumps rubella
ND-R	number-of-doses recorded
OPV	oral polio vaccine
OR	odds ratio

SD standard deviation
UTD-V up-to-date by valid doses

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Table 1

Study population characteristics by birth country

Country	Total studied		Female gender		Age at adoption (in months)		Age at initial visit (in months)		Non- institutionalized ^a		Adequately nourished ^b		Any record ^c	
	n	%	n	%	Median	Range	Median	Range	n	%	n	%	n	%
Russia	236	(42)	97	(41)	16	5–200	17	6–201	10	(4)	148	(63)	214	(91)
China	146	(26)	133	(91)	13	8–104	14	9–105	18	(12)	103	(71)	136	(93)
Guatemala	89	(16)	37	(42)	9	5–118	9	5–118	68	(76)	78	(88)	84	(94)
Kazakhstan	50	(9)	23	(46)	12	7–173	12	7–173	2	(4)	41	(82)	49	(98)
South Korea	41	(7)	17	(42)	8	5–27	8	5–28	39	(95)	40	(98)	41	(100)
Total	562	(100)	307	(55)	13	5–200	13	5–201	137	(24)	410	(73)	524	(93)

^aChildren institutionalized less than 6 months were considered non-institutionalized.

^bWeight-for-age z-score two or more SDs below the mean was used as a surrogate for malnutrition. Values above this cutoff were defined as adequately nourished.

^cAny documentation of immunizations from the child's birth country.

Table 2

Assessment documented immunizations by vaccine antigen

	Diphtheria (N = 531)		Tetanus (N = 535)		Polio (N = 505)		Hepatitis B (N = 517)		Measles (N = 276)		Mumps (N = 236)		Rubella (N = 224)		Varicella (N = 277)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Not up-to-date and valid (total)	223	(42)	226	(42)	105	(21)	192	(37)	51	(18)	59	(25)	91	(41)	145	(52)
No record	35	(7)	35	(7)	29	(6)	35	(7)	13	(5)	12	(5)	11	(5)	11	(4)
Incorrect dates																
Date does not exist	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Date recorded prior to date of birth	2	(<1)	2	(<1)	1	(<1)	2	(<1)	0	(0)	0	(0)	0	(0)	0	(0)
Date recorded after adopt date	2	(<1)	2	(<1)	0	(0)	3	(1)	0	(0)	0	(0)	0	(0)	0	(0)
Date is unknown	10	(2)	10	(2)	9	(2)	8	(2)	1	(<1)	1	(<1)	1	(<1)	0	(0)
Vaccine given too early	7	(1)	7	(1)	17	(3)	2	(<1)	19	(7)	2	(1)	1	(<1)	0	(0)
Interval between doses is too short	9	(2)	10	(2)	2	(<1)	7	(1)	0	(0)	0	(0)	0	(0)	0	(0)
Not enough doses	161	(30)	163	(30)	55	(11)	141	(27)	18	(7)	44	(19)	78	(35)	134	(48)
Inappropriate vaccination given for age	12	(2)	12	(2)	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a
Up-to-date and valid (total)	308	(58)	309	(58)	400	(79)	325	(63)	225	(82)	177	(75)	133	(59)	132	(48)

^aNot applicable.

Table 3a

Proportion of children with protective antibody levels

	Total	>3 recorded doses		Up-to-date and valid record		
		N	n	(%)	n	(%)
Diphtheria						
Russia	223	125	(87)	83	(84)	
China	134	102	(76)	93	(76)	
Guatemala	87	71	(94)	67	(96)	
Kazakhstan	49	39	(79)	28	(75)	
South Korea	38	27	(96)	37	(97)	
Total	531	364	(85)	308	(85)	
Tetanus						
Russia	226	126	(94)	84	(93)	
China	136	104	(90)	94	(91)	
Guatemala	87	71	(99)	67	(99)	
Kazakhstan	48	38	(95)	27	(96)	
South Korea	38	27	(100)	37	(100)	
Total	535	366	(95)	309	(95)	
Polio						
Russia	209	130	(97)	152	(94)	
China	130	107	(85)	109	(85)	
Guatemala	84	71	(90)	71	(92)	
Kazakhstan	47	40	(98)	34	(94)	
South Korea	35	25	(96)	34	(97)	
Total	505	373	(92)	400	(92)	
Hepatitis B						
Russia	226	80	(89)	114	(79)	
China	130	74	(76)	88	(73)	
Guatemala	79	53	(89)	58	(88)	
Kazakhstan	45	31	(61)	29	(66)	
South Korea	37	28	(64)	36	(58)	

Note: It is possible for the number of children who have records that are up-to-date and valid to exceed the number of children with >3 doses since depending on the age of the child, a child with <3 doses may be considered up-to-date.

Total		<u>>3 recorded doses</u>		<u>Up-to-date and valid record</u>	
	<i>N</i>	<i>n</i>	(%)	<i>n</i>	(%)
Total	517	266	(79)	325	(75)

Table 3b

Proportion of children with protective antibody levels

	Total	>3 recorded doses		Up-to-date and valid record		
		N	n	(%)	n	(%)
Measles						
Russia	143	96	(92)	120	(78)	
China	77	61	(95)	54	(87)	
Guatemala	28	24	(100)	25	(92)	
Kazakhstan	20	14	(100)	18	(78)	
South Korea	8	6	(100)	8	(88)	
Total	276	201	(95)	225	(82)	
Mumps						
Russia	125	82	(68)	100	(53)	
China	59	8	(38)	31	(16)	
Guatemala	25	22	(86)	22	(86)	
Kazakhstan	19	13	(85)	16	(63)	
South Korea	8	6	(83)	8	(63)	
Total	236	131	(72)	177	(52)	
Rubella						
Russia	117	45	(96)	66	(67)	
China	56	6	(50)	32	(16)	
Guatemala	24	22	(91)	21	(90)	
Kazakhstan	19	2	(100)	6	(0)	
South Korea	8	6	(100)	8	(88)	
Total	224	81	(91)	133	(56)	
Varicella						
Russia	144	0	(-)	51	(29)	
China	75	0	(-)	45	(0)	
Guatemala	28	13	(38)	21	(29)	
Kazakhstan	22	1	(100)	8	(13)	
South Korea	8	5	(20)	7	(14)	

Total		<u>>3 recorded doses</u>		<u>Up-to-date and valid record</u>	
<i>N</i>		<i>n</i>	(%)	<i>n</i>	(%)
Total		277	19 (37)	132	(17)

Note: It is possible for the number of children who have an up-to-date and valid record to exceed the number with >1 doses since children who are not yet past the age at which they would be considered late for their first dose, they are considered up-to-date and valid.

Table 4a

Univariate analyses for protective levels of antibody by vaccine antigen

Variables	Diphtheria		Tetanus		Polio		Hepatitis B	
	OR	(95% CI) ^d	OR	(95% CI) ^d	OR	(95% CI) ^d	OR	(95% CI) ^d
Birth country ^b								
China	0.21	(0.09–0.47)	0.11	(0.03–0.40)	0.59	(0.26–1.35) ^c	0.54	(0.30–1.00) ^d
Kazakhstan	0.45	(0.16–1.26) ^c	0.38	(0.07–2.03) ^c	2.70	(0.56–13.06) ^c	0.45	(0.21–0.98) ^d
Russia	0.44	(0.20–0.97)	0.25	(0.07–0.96)	1.27	(0.55–2.96) ^c	0.59	(0.33–1.04) ^d
South Korea	3.75	(0.45–31.07) ^c	2.25	(0.10–49.63) ^c	4.08	(0.50–33.50) ^c	0.48	(0.21–1.08) ^d
Male	1.42	(0.92–2.20)	1.20	(0.69–2.10)	1.57	(0.87–2.84)	0.97	(0.68–1.38)
Increasing age (by year)	1.04	(0.92–1.18)	1.18	(0.95–1.47)	2.03	(1.26–3.26)	0.91	(0.83–1.00)
Non-institutionalized	3.00	(1.58–5.67)	3.04	(1.27–7.26)	1.64	(0.78–3.48)	1.61	(1.04–2.48)
Adequately nourished	1.59	(1.01–2.51)	2.28	(1.3–4.00)	1.99	(1.10–3.60)	1.19	(0.80–1.77)
Any documentation	4.44	(2.20–8.96)	5.28	(2.46–11.31)	1.43	(0.48–4.27)	2.65	(1.32–5.35)
Number of recorded doses (ND-R)								
1 vs. 0	3.05	(1.20–7.81)	4.33	(1.48–12.67)	0.81	(0.28–2.39) ^c	1.94	(0.95–3.97) ^c
2 vs. 0	7.20	(3.08–16.85)	29.17	(6.59–128.99)	1.96	(0.64–6.01) ^c	3.58	(2.01–6.37)
3 vs. 0 ^e	5.97	(3.33–10.70)	11.99	(6.07–23.68)	2.97	(1.30–6.75)	8.91	(5.41–14.69)
≥4 vs. 0	7.24	(3.27–16.06)	36.25	(8.23–159.74)				
Up-to-date and valid (UTD-V)	2.00	(1.30–3.09)	4.06	(2.21–7.44)	2.23	(1.20–4.13)	4.57	(3.12–6.71)

^a 95% confidence interval.

^b Guatemala is the reference country.

^c The overall test was significant for birth country indicating that at *least one* country was different. Each country was then examined individually and countries with the value of one within the 95% CI were not significantly different from the reference group.

^d The overall test was not significant for birth country. However, values were entered for consistency.

^e Equal to ≥3 or more vs. 0 for Polio and Hepatitis B.

Table 4b

Univariate analyses for protective levels of antibody by vaccine antigen

Variables	Measles		Mumps		Rubella		Varicella	
	OR	(95% CI) ^d	OR	(95% CI) ^d	OR	(95% CI) ^d	OR	(95% CI) ^d
Birth country ^b								
China	0.52	(0.11–2.51) ^c	0.04	(0.01–0.15)	0.02	(<0.01–0.08)	0.25	(0.09–0.74)
Kazakhstan	0.23	(0.04–1.34) ^c	0.33	(0.08–1.35) ^d	0.01	(<0.01–0.08)	0.79	(0.23–2.70) ^d
Russia	0.26	(0.06–1.14) ^c	0.24	(0.08–0.75)	0.15	(0.03–0.65)	1.60	(0.68–3.77) ^d
South Korea	0.54	(0.04–6.84) ^c	0.32	(0.05–1.90) ^d	0.64	(0.05–8.12) ^d	0.30	(0.03–2.83) ^d
Male	0.76	(0.42–1.40)	1.18	(0.71–1.97)	1.98	(1.17–3.37)	1.22	(0.73–2.03)
Increasing age (by year)	2.61	(1.61–4.24)	1.62	(1.33–1.98)	1.46	(1.22–1.75)	1.38	(1.21–1.58)
Non-institutionalized	1.15	(0.45–2.94)	1.95	(0.89–4.27)	2.26	(1.01–5.09)	0.44	(0.17–1.10)
Adequately nourished	1.43	(0.76–2.68)	1.87	(1.07–3.28)	2.49	(1.38–4.48)	1.26	(0.72–2.19)
Any documentation	2.40	(0.91–6.29)	1.83	(0.69–4.82)	1.44	(0.53–3.93)	0.89	(0.35–2.30)
Number of recorded doses (ND-R)								
≥1 vs. 0	19.74	(9.25–42.14)	8.13	(4.51–14.64)	30.28	(12.81–71.61)	1.32	(0.50–3.48)
Up-to-date and valid (UTD-V)	1.27	(0.60–2.69)	1.28	(0.71–2.32)	1.98	(1.15–3.40)	0.27	(0.16–0.48)
History of disease	NA ^e		NA ^e		NA ^e		20.22	(9.16–44.63)

^a95% confidence interval.

^bGuatemala is the reference.

^cThe overall test was not significant for birth country. However, values were entered for consistency.

^dThe overall test was significant for birth country indicating that at *least one* country was different. Each country was then examined individually and countries with the value of one within the 95% CI were not significantly different from the reference group.

^eNot applicable.

Multivariable analysis models to determine factors associated with protective antibody for diphtheria, tetanus, polio and hepatitis B

Table 5a

Variable	Multivariable statistical model			
	Number-of-doses-recorded (ND-R) model ^d		Up-to-date and valid (UTD-V) model ^b	
	OR	(95% CI) ^c	OR	(95% CI) ^c
Diphtheria				
China ^d	0.23	(0.10–0.53)	0.21	(0.09–0.47)
Any record	NS ^e		4.32	(2.08–8.95)
1 vs. 0 doses	2.63	(1.01–6.87)	NA ^f	
2 vs. 0 doses	5.32	(2.22–12.78)	NA ^f	
3 vs. 0 doses	5.88	(3.15–10.99)	NA ^f	
≥4 vs. 0 doses	6.36	(2.82–14.33)	NA ^f	
UTD-V	NA ^d		NS ^e	
AIC ^g		476.31		492.16
Tetanus				
China ^d	0.12	(0.03–0.47)	0.12	(0.03–0.48)
Adequately nourished	NS ^e		1.88	(1.03–3.44)
Any record	NS ^e		2.82	(1.21–6.57)
1 vs. 0 doses	3.32	(1.13–9.76)	NA ^f	
2 vs. 0 doses	16.55	(4.30–63.69)	NA ^f	
3 vs. 0 doses	11.63	(5.56–24.31)	NA ^f	
≥4 vs. 0 doses	25.84	(6.68–99.89)	NA ^f	
UTD-V	NA ^f		3.82	(1.90–7.66)
AIC ^g		273.52		301.43
Polio				
Kazakhstan ^d	NS ^e		6.64	(1.09–40.43)
Increasing age (in years)	2.44	(1.35–4.41)	2.55	(1.41–4.60)
Non-institutionalized	3.25	(1.06–9.95)	3.32	(1.08–10.21)

Variable	Multivariable statistical model			
	Number-of-doses-recorded (ND-R) model ^a		Up-to-date and valid (UTD-V) model ^b	
	OR	(95% CI) ^c	OR	(95% CI) ^c
≥3 vs. 0 doses	3.44	(1.39–8.52)	NA ^f	
UTD-V	NA ^f		2.70	(1.37–5.32)
AIC ^g		309.58		308.91
Hepatitis B				
2 vs. 0 doses	3.58	(2.01–6.37)	NA ^f	(0.03–0.48)
≥3 vs. 0 doses	8.91	(5.41–14.69)	NA ^f	(1.03–3.44)
UTD-V	NA ^f		4.57	(3.12–6.71)
AIC ^g		604.01		625.34

^aModel that includes number-of-doses recorded (ND-R) as the definition of vaccination status.

^bModel that includes up-to-date and valid (UTD-V) as the definition of vaccination status.

^c95% confidence interval.

^dGuatemala is the reference country.

^eNot significant.

^fNot applicable.

^g“Best fit” model as determined by AIC is bolded.

Multivariate analysis models to determine factors associated with protective antibody for measles, mumps, rubella, and varicella

Table 5b

Variable	Multivariable statistical model			
	Number-of-doses-recorded (ND-R) model ^d		Up-to-date and valid (UTD-V) model ^b	
	OR	(95% CI) ^c	OR	(95% CI) ^c
Measles				
Russia ^d	NS ^e		0.19	(0.04–0.90)
Increasing age (in years)	1.72	(1.12–2.66)	3.29	(1.92–5.62)
≥1 vs. 0 doses	14.2	(6.47–31.14)	NA ^f	
UTD ^g	NA ^f	(3.15–10.99)	NS ^e	
AIC ^h		184.55		226.56
Mumps				
China ^d	0.11	(0.03–0.43)	0.04	(0.01–0.16)
Russia ^d	0.26	(0.08–0.87)	0.20	(0.06–0.65)
Increasing age (in years)	1.47	(1.21–1.79)	1.59	(1.30–1.95)
≥1 vs. 0 doses	3.98	(2.01–7.88)	NA ^f	
AIC ^h		253.39		267.32
Rubella				
China ^d	0.08	(0.01–0.58)	0.02	(<0.01–0.11)
Kazakhstan ^d	<0.01	(<0.01–0.59)	<0.01	(<0.01–0.08)
Russia ^d	NS ^e		0.16	(0.03–0.77)
Increasing age (in years)	1.54	(1.25–1.89)	1.81	(1.43–2.29)
≥1 vs. 0 doses	20.98	(7.96–55.29)	NA ^f	
UTD-V	NA ^f		4.21	(1.83–9.69)
AIC ^g		169.39		209.44
Varicella				
Increasing age (in years)	1.35	(1.16–1.57)	1.22	(1.03–1.44)
History of disease	18.38	(8.13–41.53)	19.32	(8.36–44.65)
UTD-V	NA ^f		0.42	(0.20–0.91)

Variable	Multivariable statistical model			
	Number-of-doses-recorded (ND-R) model ^a		Up-to-date and valid (UTD-V) model ^b	
	OR	(95% CI) ^c	OR	(95% CI) ^c
AIC ^g				253.07

^aModel that includes number-of-doses recorded (ND-R) as the definition of vaccination status.

^bModel that includes up-to-date and valid (UTD-V) as the definition of vaccination status.

^c95% confidence interval.

^dGuatemala is the reference country.

^eNot significant.

^fNot applicable.

^g“Best fit” model as determined by AIC is bolded.