Predictive Value of Immunization Records and Risk Factors for Immunization Failure in Internationally Adopted Children

Emaculate Verla-Tebit, PhD; Xiaobei Zhu, MS; Eva Holsinger, MD; Anna Maria Mandalakas, MD, MS

Objectives: To measure the predictive value of immunization records for protective immunity and identify risk factors for immunization failure.

Design: Prospective cross-sectional study, 2001-2006.

Setting: International Adoption Clinic, Rainbow Babies and Children's Hospital, Cleveland, Ohio.

Participants: A total of 465 international adoptees presenting within 180 days of arrival.

Main Exposure: Immunization records of vaccines given.

Outcome Measures: Protective immunity to polio, hepatitis B, tetanus, diphtheria, and measles.

Results: Vaccination records were available for 397 (85.4%) adoptees (mean age, 19.4 months; 65.2% girls). Most children came from Russia (41.7%), China (20.9%), and Guatemala (15.7%). Acute or chronic malnutrition was present in 5.5% and 15.4% of adoptees, respectively. Preadoptive settings were institutional (52%), community-based (14%), or both (34%). Of adoptees with 3 or more tetanus (n=203) or 3 or more diphtheria (n=205) vaccinations, 87.2% and 94.6% had protective immunity, respectively. Of adoptees with 3 or more polio vaccinations (n=216), protective immunity was present in 58.3%, 82.4%, and 51.9% for polio types 1, 2, and 3, respectively. Of adoptees with 2 or more hepatitis B vaccinations (n=170), 94.1% had protective immunity. A total of 80.8% of adoptees with measles vaccination (n=99) had protective immunity. Children from China were less likely to have protective immunity than children from Russia (odds ratio, 0.34; 95% confidence interval, 0.17-0.66). Nutritional status had no predictive effect.

Conclusions: The predictive value of immunization records in international adoptees is limited and varies between birth countries. Immunization records should not be accepted as evidence of protective immunity. Parents should be well informed and supported to choose between revaccination or vaccination, based on serologic testing.


In the past 15 years, more than 247,000 foreign-born children have been adopted by families in the United States. Many of these children have lived in institutional settings that are crowded and resource-poor. As a result, these children often suffer from malnutrition, which may lead to an increased risk of immunization failure. Foreign-born children, including international adoptees, are more likely to be underimmunized than US-born children. International adoptees often have incomplete or no written immunization records.

According to the Red Book, "Written documentation of immunization can be accepted as evidence of adequacy of previous immunization if the vaccines, dates of administration, number of doses, intervals between doses, and age of the child at the time of immunization are consistent internally and comparable to current US or World Health Organization schedules."

Although the American Academy of Pediatrics Committee on Infectious Diseases advises that valid written records of vaccination could be considered as evidence of previous vaccination, these records, especially for children from orphanages, may not accurately reflect vaccine-induced protective immunity. Reasons for this include documentation inaccuracies, lack of vaccine potency, and impaired immune response, possibly due to stress or malnutrition.

Previous studies on the predictive value of immunization records in international adoptees have had small sample sizes and inconsistent findings. Very few studies have examined factors that could in-
fluence the relationship between vaccination records and protective immunity such as the birth country, nutritional status, and preadptive settings. We conducted a prospective cross-sectional study to measure the predictive value of vaccination records for protective immunity in international adoptees and to identify risk factors for immunization failure.

 METHODS

Cross-sectional data was obtained from international adoptees presenting for care at the International Adoption Clinic of Rainbow Babies and Children's Hospital between January 2001 and April 2006. Children were included in the study if they presented within 180 days of arrival in the United States, did not have hepatitis B, hepatitis C, or human immunodeficiency virus infections, and their adoptive parents completed written informed consent. Children were excluded in subanalysis of specific vaccine types if they had received that particular vaccine in the United States. The study protocol was approved by the institutional review board of University Hospitals of Cleveland.

Medical records were reviewed for relevant history and detailed vaccination history, which included the number of vaccines and the dates received. Information was obtained on demographic characteristics, preadpective care history, and longitudinal anthropometric measures. Preadaptive settings were described as either exclusively community (foster care or care within the biologic family), exclusively institutional (orphanage and hospital-based care), or combined institutional and community-based care. A vaccine dose was considered valid when the written vaccine record was available and included the type of vaccine and specified the date of administration. A specific recorded vaccine dose was considered invalid when no administration date was recorded or when the date of administration preceded the child's date of birth. Children with invalid vaccine doses were excluded from the analysis.

A venous blood sample was obtained and used to determine serum antibody titers to hepatitis B, measles, diphtheria, tetanus, and polio types 1 through 3. Serum antibody titers were measured using enzyme-linked immunosorbent assay (ELISA) for diphtheria, tetanus, and measles or enzyme immunosassay for hepatitis B and neutralizing antibody titers for polio under standard procedures in accredited medical laboratories. Serum antibody titers were not obtained for all the children, as some parents chose to revaccinate their children rather than measure antibody titers, while others had antibody titers measured somewhere else. The total number of children analyzed for each vaccine type therefore depended on the number who had titers ordered, did not have a vaccination in the United States, and had valid vaccine doses. These numbers differ for each vaccine type.

Laboratory-specific definitions of protective immunity were used as follows: tetanus, 0.5 IU/mL or more; diphtheria, 0.1 IU/mL or more; polio, titers of 1:40 or more; measles, more than 1.1 IU/mL; hepatitis B surface antibody, index 10 IU/mL or more. We developed a surrogate measure of protective immunity that measured acquired immunity most likely due to vaccine administration rather than immunity acquired from the environment secondary to infection or to exposure to the disease. We defined this surrogate measure as immunity to both tetanus (teta

 RESULTS

A total of 492 international adoptees presented for care during the study period. Twenty-seven were excluded because they presented more than 180 days after arrival in the United States (n = 22), were infected with hepatitis B virus (n = 4), or were infected with hepatitis C virus (n = 1). Therefore, the study sample included 465 children.

Characteristics of the study sample are presented in Table 1. Vaccination records were available for 397 (85.4%) adoptees. The mean (SD) age at adoption was 19.4 (19.2) months (range, 4-144 months), with 65.2% girls. Most of the adoptees came from Russia (41.7%), China (20.9%), and Guatemala (15.7%), and 81% presented to the clinic within 30 days of arrival (mean [SD], 23.1 [21.0] days; range, 1-148 days). On presentation to the clinic, 5.5% and 15.4% of the adoptees had evidence of moderate to severe acute (wasting) or chronic (stunting) malnutrition, respectively. Preadaptive settings were exclusively institutional (52%), exclusively community-based (14%), or a combination of institutional and community-based (34%). The parents of 97 children (20.9%) chose to revaccinate their children rather than measure protective immunity, while another 48 (10.3%) had serum antibody titers done elsewhere.

Table 2 displays the results of protective immunity to each vaccine type stratified by the number of valid vaccine doses recorded. Adoptees had a mean (SD) of 2.1 (1.4) tetanus/diphtheria vaccinations (range, 0-4). For adoptees with 3 or more tetanus (n = 203) or 3 or more diphtheria (n = 205) vaccinations, 87.2% and 94.6% had evidence of protective immunity, respectively. Adoptees had a mean (SD) of 2.3 (1.5) polio vaccinations (range,
For adoptees with 3 or more polio vaccinations (n=99), 80.8% of them had evidence of protective immunity. Twenty of these children received a measles vaccine before 1 year of age, with 75.0% developing protective immunity.

Table 3 presents results of bivariate analysis stratified by the number of valid vaccines recorded for each vaccine type. When comparing across birth countries using the χ² test, children born in China with 3 or more doses of the DPT or polio subtype I were less likely to have protective immunity than children with 3 or more doses of DPT or polio subtype I born in other countries. When comparing between children from different preadoptive settings, there were no significant differences between protective immunity within vaccine dose number strata. Similarly, there was no significant difference in protective immunity within vaccine dose number strata between children with and without moderate to severe stunting or wasting at presentation (data not shown).

The results of multivariate regression are presented in Table 4. Children from China, Guatemala, and “other” countries were less likely to have protective immunity to hepatitis B vaccine compared with children from Russia (OR, 0.72; 95% CI, 0.20-2.63; OR, 0.59; 95% CI, 0.07-4.69; and OR, 0.29, 95% CI, 0.10-0.87, respectively). Children from China had 80% and 64% increased risk of lacking protective immunity to tetanus and polio type 1, respectively, compared with children from Russia (OR, 0.20; 95% CI, 0.08-0.49 and OR, 0.36; 95% CI, 0.19-0.71, respectively). Our findings also suggest that children from China may have been more likely to have protective immunity to measles compared with children from Russia (OR, 2.23; 95% CI, 0.95-5.21; P=.08). Birth country was not predictive of protective immunity with respect to diphtheria and polio types 2 and 3. Regarding surrogate immunity, defined as protective immunity to both tetanus and polio type 1, children from China were 66% less likely to have protective immunity compared with children from Russia (OR, 0.34; 95% CI, 0.17-0.66).

Children who lived exclusively in the community were nearly 7-fold more likely to have protective immunity to tetanus compared with those who lived in both institutional and community settings (OR, 6.69; 95% CI, 1.40-31.9) (Table 4). Preadoptive setting was not predictive of protective immunity in any other regression models.
Other studies have reported a range of immunity (35%-tive immunity to diphtheria and tetanus, respectively. vaccinations, 94.6% and 87.2% of children had protective immunity derived from natural infection in international adoptees. Consistent with reports from previous studies, our study demonstrates that immunization records for international adoptees may not accurately predict the presence of protective immunity. Our findings also suggest that birth country and pre-adoptive environment may be associated with a child’s likelihood of having protective immunity. For children with 3 or more documented valid DPT vaccinations, 94.6% and 87.2% of children had protective immunity to diphtheria and tetanus, respectively. Other studies have reported a range of immunity (35%-88%) to DPT, with varying results likely owing to differences in the reliability of methods used to determine titers. A more recent study by Viviano and colleagues, who used neutralizing antibody titers (diphtheria) and ELISA (tetanus), showed that for 70 international adoptees in Italy with 3 or more vaccine doses, 85.7% and 72.8% (using cutoffs of 0.1 and 0.5 IU/mL for diphtheria and tetanus, respectively, as used in our study) had evidence of protective immunity to diphtheria and tetanus, respectively.

Regarding polio, we observed in our study that for children with 3 or more polio doses, 58.3%, 82.4%, and 51.9% had protective immunity to polio types 1, 2, and 3, respectively. Miller and colleagues observed that for children from both community and institutional settings with 3 or more polio doses, only 58%, 65%, and 62% had evidence of protective immunity to polio types 1, 2, and 3, respectively, while Schulpen and colleagues observed that 71%, 94%, and 79% had protective immunity to polio
types 1, 2, and 3, respectively (preadoptive setting not specified). Both studies used neutralizing antibody, as used in our study (considered to be the most specific test for determining the protective antibody response to polio virus). Viviano and colleagues also used neutralizing antibody and observed that 67.1%, 91.4%, and 42.8% of children in institutional settings had full protection against polio types 1, 2, and 3, respectively, after 3 or more doses. We observed better protective immunity to polio type 2 compared with types 1 and 3, which is similar to what has been reported previously. The reason for this is unclear, although it has been suggested that type 2 polio vaccine virus and enteric pathogens often interfere with the immune response to types 1 and 3.

Regarding hepatitis B, we observed that 94.1% of 170 children with 2 or more vaccines had evidence of protective immunity compared with 68.9% reported by Viviano et al and 69% reported by Saiman et al. Because all 3 studies used similar methodologies to measure antibody titers, we suspect that differences in the rates of protective immunity may be related to variable documentation of preadoptive vaccination.

We observed protective immunity in 80.8% of 99 children who had received at least 1 measles vaccine, while Miller et al reported 90% protection. Although most of the children in both studies emigrated from Russia and China, the average age of arrival reported by Miller et al was 38.2 months, compared with 19.4 months in our study. The risk of infection for measles increases with age, and older children may have received more doses of the measles vaccine, both of which may account for the higher protection rate observed in our study.

Our study indicates that the documented immunization records of international adoptees may not accurately reflect immunity. Reasons that have been proposed include falsification of vaccine certificates, inaccurate entries, and lack of vaccine potency. In our study, we examined protective immunity in children without documented immunization and observed that 43% to 84% of these children had protective immunity to either hepatitis B, measles, diphtheria, tetanus, or polio types 1, 2, or 3. The presence of protective immunity in these children may reflect poor documentation of vaccination coverage. This has been illustrated in previous studies evaluating international adoptees for Bacille Calmette Guerin immunization. For children younger than 12 months without documented vaccination, persistent maternal antibodies may also account for the presence of protective immunity. In our study, 67.7% of children older than 12 months and 80.0% of children younger than 12 months without documented vaccination had protective immunity to hepatitis B.

We further looked at protective immunity, with emphasis on country of origin. Children from China were significantly less likely to have protective immunity to tetanus or polio type 1 after 3 or more doses of DPT or polio vaccine compared with children from Russia, Guatemala, and other countries. After controlling for number of doses of vaccine, preadoptive settings, and sex, logistic regression models also indicated that children from China had 80% and 64% greater risk of lacking protective immunity to tetanus and polio type 1, respectively, than children from Russia. This finding is consistent with results of Schulpen et al, who also noted in an unpublished source that vaccination certificates from China seemed unreliable because many were written with the same pencil, given on the same date of consecutive months, or dated before the birth of the child. Our study also shows that children from China are more likely to have protective immunity against measles than children from Russia. This may be owing to immunity acquired from the disease rather than from immunization because protective immunity to measles for children without a documented measles vaccine was 62.5% for Chinese adoptees compared with 44.9% of Russian adoptees; it could also be owing to lack of documentation, as explained above. Data showing protective immunity in US children following vaccination reveals close to 100% protective immunity 1 month after completing 3 doses of vaccine (diphtheria, 99.4%; tetanus, 100%; polio types 1, 2, and 3, 100% for each type; hepatitis B, 98.2%). Of note, international adoptees in our and other studies had immunization titers drawn following adoption and irrespective of the time of vaccination. Although this delay

---

Table 4. Multivariate Regression Models With OR (95% CI) of Protective Immunity to Hepatitis, Measles, Polio Types 1 Through 3, Diphtheria, and Tetanus

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Country of Origin</th>
<th>Protective Immunity, OR (95% CI) a</th>
<th>Preadoptive Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Russia</td>
<td>China</td>
<td>Guatemala</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.0 [Reference]</td>
<td>0.72 (0.20-2.63)</td>
<td>0.59 (0.07-4.69)</td>
</tr>
<tr>
<td>Measles</td>
<td>1.0 [Reference]</td>
<td>2.23 (0.95-5.21)</td>
<td>1.04 (0.27-3.99)</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>1.0 [Reference]</td>
<td>0.64 (0.19-2.23)</td>
<td>0.99 (0.15-6.65)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1.0 [Reference]</td>
<td>0.20 (0.08-0.49)</td>
<td>0.70 (0.17-2.81)</td>
</tr>
<tr>
<td>Polio type 1</td>
<td>1.0 [Reference]</td>
<td>0.36 (0.19-0.71)</td>
<td>0.49 (0.20-1.18)</td>
</tr>
<tr>
<td>Polio type 2</td>
<td>1.0 [Reference]</td>
<td>0.53 (0.23-1.23)</td>
<td>1.69 (0.47-6.12)</td>
</tr>
<tr>
<td>Polio type 3</td>
<td>1.0 [Reference]</td>
<td>0.62 (0.32-1.21)</td>
<td>0.89 (0.37-2.17)</td>
</tr>
<tr>
<td>Surrogate immunity b</td>
<td>1.0 [Reference]</td>
<td>0.34 (0.17-0.66)</td>
<td>0.45 (0.18-1.13)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a All models adjusted for sex and number of vaccine doses.

b Surrogate immunity is defined as protective immunity to both polio and tetanus.
in measurement may account for a portion of the lowered rates of protective immunity found in international adoptees, we suspect that the vaccine’s diminished protective efficacy results from a number of other factors including breaks in the cold chain, malnutrition, and errors in documentation.

We derived a single surrogate measure of immune status most likely due to immunization rather than environmental exposure or infection, as described earlier, namely protective immunity to both tetanus and polio type 1. Using this surrogate measure, we observed that children from China were at a 66% increased risk of lacking protective immunity compared with children from Russia after adjusting for number of vaccine doses, sex, and preadoptive settings. Primary care physicians dealing with this group of children should always consider measuring antibody titers to assess immune status rather than considering immunization records, even if these records appear to be valid and complete. Revaccinating these children may be a cost-effective option for parents or caregivers who prefer this to having blood drawn to measure antibody titers. Consistent with this approach, parents of children in our study chose to revaccinate from 5% to 21% of the time, depending on the vaccination under consideration. Although repeating the vaccines is generally reported as safe, the rate of serious local reactions after DPT vaccine increases with the number of doses administered and the economic effects of vaccines are frequently underestimated and unrecognized. Hence, revaccination may not be the most appropriate option for every immunization or every family.

Malnutrition at the time of vaccination may decrease vaccine efficacy, as malnutrition is associated with immune suppression. Hence, internationally adopted children from resource-poor settings may have increased risk of immunization failure. We explored the effect of preadoptive settings and nutritional status on the relationship between vaccination record and protective immunity. We observed no significant differences in protective immunity related to nutritional status, consistent with findings from a previous study. Nevertheless, in our study anthropometric measurements obtained at the time of presentation to our clinic only serve as a surrogate measure for nutritional status at the time of vaccination. Studies have repeatedly demonstrated rapid physical growth in international adoptees in the immediate postadoptive period. Because children presented to our clinic an average of 30 days after arrival in the United States and 6 weeks after joining their adoptive families, nutritional status at the time of presentation to the clinic is likely a poor surrogate measure of nutritional status at the time of vaccination.

In our study, children who lived exclusively in the community were nearly 7-fold more likely to have protective immunity to tetanus compared with children who lived in both institutional and community settings. Hostetter and Johnson also observed that only 12% of children who lived in orphanages had protective immunity to diphtheria and tetanus compared with 78% of children who had lived in the local community.

Strengths of our study include the large sample size and the comprehensive nature in which we assessed a wide range of vaccines, including other factors that could influence the relationship between immunization record and protective immunity. Limitations of our study include the lack of verification of the immunization records from the country of adoption and the inability to differentiate between protective immunity derived from infection compared with vaccination. Nevertheless, our use of a surrogate measure of immunity provided a method to overcome this barrier. Finally, although we had a large sample size that supported our regression analysis, we had small numbers in some of our stratified analyses, limiting our ability to draw conclusions from these subgroups.

Our results suggest that the predictive value of immunization records in international adoptees may be limited and associated with birth country. Written immunization records overestimate the prevalence of protective immunity. Although documented valid vaccinations may support interpretation of serum antibody titers and guide the subsequent vaccination process, these records should not be accepted as evidence of protective immunity. For each vaccine under consideration, parents should be well informed and supported to choose between revaccination that disregards the written record or vaccination based on results of serum antibody testing.

Accepted for Publication: September 5, 2008.

Correspondence: Anna M. Mandalakas, MD, MS, Global Child Health, Iris S. and Bert Wolstein Research Bldg, 2103 Cornell Rd, Ste 6212, Cleveland, OH 44106-7292 (anna.mandalakas@case.edu).

Author Contributions: Study concept and design: Mandalakas. Acquisition of data: Holsinger and Mandalakas. Analysis and interpretation of data: Verla-Tebit, Zhu, and Mandalakas. Drafting of the manuscript: Verla-Tebit and Mandalakas. Critical revision of the manuscript for important intellectual content: Verla-Tebit, Zhu, Holsinger, and Mandalakas. Statistical analysis: Verla-Tebit and Zhu. Obtained funding: Mandalakas. Administrative, technical, and material support: Verla-Tebit and Mandalakas. Study supervision: Mandalakas.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grant IK23-HD40982 from the National Institutes of Health (Dr Mandalakas).

Additional Contributions: The authors graciously thank the families and staff of the Adoption Health Service at Rainbow Babies and Children’s Hospital. Special thanks are given to Najla Golebierski, BA.

REFERENCES


