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Internationally adopted children: What vaccines should they receive?

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ABSTRACT

It is of paramount importance to know the vaccination status in internationally adopted children, so that they can be correctly immunized. This study ascertains the seroprotection rate for vaccine-preventable diseases and the validity of the immunization cards in 637 adopted children. The absence of the immunization card (13% of children) correlated with a poor global vaccine protection. Children with immunization records (87%) had a better global seroprotection but the information obtained from the card did not accurately predict seroprotection for each particular antigen. The best variable to predict the status of seroprotection was the country of origin. The highest rate of protection was found in children from Eastern Europe and, in descending order, India, Latin America, China and Africa. General recommendations for immunization of internationally adopted children are difficult to establish. Actions for vaccination have to be mainly implemented on the basis of the existence of the immunization card and of the country of origin.

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1. Introduction

During the last decade the number of internationally adopted children has been continuously increasing [1,2]. According to the data of the Spanish Department of Social Services, more than 30,000 foreign children have been adopted in Spain over the last 10 years making Spain the second country in absolute numbers of international adoptions, only preceded by the USA. Information on these children is limited and it is difficult to ascertain their medical problems [3,4]. In their initial assessment, one of the main concerns is their immunization status. A significant number of adopted children arrive with vaccination documents [2–6], and a major issue is to determine whether they have developed adequate protection against the diseases for which they have supposedly been vaccinated. There have been few published studies about the immunization status of internationally adopted children [7-12], and it is difficult to generalize about the results, mainly because of the low number of children from each of the different countries. Moreover, the lack of common criteria for assessing the validity of vaccine documentation, differences in laboratory techniques and the cut-off values used to evaluate serological immune response, have further contributed to confound and complicate the situation. Because of the absence of predictive factors for immune vaccine protection, the common final conclusion in all these reports has emphasized the advisability of performing serological studies of vaccine protection for all internationally adopted children in order to ensure proper immunization, at least until there are more exhaustive studies.

In relation to vaccination documents, the American Academy of Paediatrics (AAP) [13] has established the essential conditions for considering these records as valid, and previous articles report variable percentages of valid documentation according to these criteria [12,14–16], even taking into account the differences between the validity and the adequacy of the records.

The main objective of this study was to determine the rate of serological protection against immune-preventable diseases (poliovirus 1, 2, 3, tetanus, diphtheria, measles, mumps, rubella and hepatitis B) for a large number of internationally adopted children. The second objective was to relate the results to independent variables: country of origin, age, type and timing of previous setting, type of vaccine and vaccination data referred to in the vaccine documentation. The clinical, nutritional and immunological statuses

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were also studied for all of the children to verify their possible interference with vaccine protection.

2. Patients and methods

This is a cross-sectional study of children carried out from April 2002 to December 2005. *Setting*: The International Adoption Clinic at the Carlos III Hospital in Madrid (Spain), a National Reference Clinic for the evaluation of adopted children. In this centre, a free health assessment is carried out in adopted children who are voluntarily taken there by their adoptive parents, such as it is recommended by the Collaborator Agencies for International Adoption in Spain. Adopted children who had received any doses of vaccine after arriving in Spain and before their first attendance at our clinic were not included in the study. Informed consent to participate in the study was requested from the parents and the protocol was approved by the Hospital's Committee of Ethics.

Demographic data were collected for all of the children, including country of origin, date of birth, age at adoption and at first medical evaluation, the setting where the child lived before adoption and the period of time of institutionalization. For methodological reasons, and according to the internal concordance of the data, we grouped the origin of the children as follows: China, India, Nepal, Eastern Europe, Latin-America (excluding Haiti), Haiti, Africa (excluding Ethiopia), and Ethiopia. Data from preadoptive immunization records were also collected: the type and number of vaccine doses received, date of administration, interval among doses, general characteristics of the records and if the number of doses was up-to-date for age. Definitions of "doses updated according to the age" were the following: children from 6 months to 12 months: 3 doses of each DTP, OPV and hepatitis B; children from 12 months to 24 months: 4 doses of each DTP and OPV, 3 doses of hepatitis B, and 1 dose of MMR; children older than 24 months: 5 doses of DTP, 4 doses of OPV, 3 doses of hepatitis B, 2 doses of MMR. According to the criteria set by the AAP [13] and confirmed by the Advisory Committee on Immunization Practice (ACIP) [17] to assess the validity of vaccine documentation, a vaccine record was considered valid when it included the type of vaccine and date of administration, with the signature or seal of the vaccine provider; all of the records which did not meet these standards were considered as non-valid.

Routine evaluation of the children included a complete medical history, a physical examination and a nutritional index (McLaren's index [18]). Laboratory testing for all of the children followed the usually recommended guidelines [2,4,6,13,19], including tests for HIV, hepatitis B (HB), hepatitis C, tuberculin skin test, intestinal parasites. Immunological status was evaluated by means of immunoglobulins and CD4 lymphocyte subsets. Tests were performed by standard methods in the laboratory of the Hospital

Specifically for this study, all the samples were tested for vaccine-preventable diseases: antibodies for poliovirus 1, 2, 3, IgG for measles, mumps and rubella viruses, as well as for diphtheria and tetanus toxoids, and HB surface antibody (HBs-Ab). The time elapsed since the children arrived in Spain until they were serologically tested was 16 days [Cl_{95%} 14.34–17.75] (S.D. 21.9 days). The assay for polioviruses was an in-house neutralization assay, using as antigen 100 TCD50 (50% tissue culture infectious dose) of each one of the virus and Hep2 Cincinnati strain. This assay has been validated in a National Seroprevalence Survey carried out in Spanish population [20]. The assays for diphtheria and tetanus toxoids specific IgG were enzyme immunoassay (ELISA) from commercial source (Virion-Serion, Germany); samples were tested diluted 1:100. Measurement of IgG for measles, mumps and rubella viruses was performed by indirect

enzyme-linked immunoabsorbent assay (ELISA) from commercial source (Enzygnost-Siemens, Germany); samples were tested diluted 1:231, as recommended by the manufacturer. The detection of HBs-Ab was made by ELISA (Abbot-Axsym). According to the international criteria [21–24], the following titres of antibodies were considered to be protective: poliovirus 1, 2 and 3: 1:2; IgG antibodies for diphtheria: >0.1 IU/mL; IgG antibodies for tetanus: >0.1 IU/mL; IgG antibodies for mumps >1:231; IgG antibodies for rubella >4 IU/mL; hepatitis B surface antigen >10 IU/L.

3. Statistical analysis

The dependent variable was the existence of serological protective titres. We performed univariate and multivariate ($\log R$) analysis with SPSS 13.0. Statistical significance was assumed for values of p < 0.05. Bivariate analysis was tested using Pearson's χ^2 or Fisher's exact tests or Student's T-test. Kappa statistics was used to assess the agreement between card information, antigen by antigen, and serologic results. Unconditional logistic regression analysis was used in order to include diverse co-variables associated with the dependent variable, thus making the autocorrelation more accurate and controlling any possibly confounding factors. A significance level of p < 0.20 was considered to include and exclude variables in the final multivariate model [25].

Serological protective titres were studied in the whole population of children, and in populations stratified for age (children younger than 12 months and children 12 months or older).

4. Results

4.1. Demographic characteristics

A total of 637 internationally adopted children were studied, 76% females [$\text{Cl}_{95\%}$ 72.8–79.5]. The mean age at adoption was 27.52 months [$\text{Cl}_{95\%}$ 25.65–29.38], with a range of 5–142 months; 240 children (37.7%) were younger than 15 months of age. Except for children from China, who had a median age of 14.09 months (S.D. ± 4.63 months), the age of the children was not significantly different according to the country of origin. The origin and main characteristics of the children are shown in Table 1. The most frequent countries of origin were China (46%), followed by India (21%) and Russia (11%). Most of the children, 89% [$\text{Cl}_{95\%}$ 86.7–91.6], had been in orphanages before adoption. The mean age at institutionalization was 8 months [$\text{Cl}_{95\%}$ 6.68–9.40], ranging from 0 to 106 months. The mean time of setting in an institution was 19.48 months [$\text{Cl}_{95\%}$ 18.36–20.59], with a range of 1–140 months.

4.2. Immunization records

In accordance with the standards of AAP [13] and ACIP [17], 466 records (73.2%) [Cl_{95%} 69.5–76.6] were considered valid, 86 (13.5%) [Cl_{95%} 10.9–16.4] non-valid and 85 children (13.3%) [Cl_{95%} 10.8–16.2] had no vaccine documentation. These figures varied depending on the areas of origin (Table 2). In most of the children (80 out of 86) with non-valid records, the reason for non-validity was the absence of signature or seal of the vaccine provider.

According to the preadoptive immunization records, the number of children updated with OPV (oral poliovirus vaccine) was 511 (80.2%) [Cl_{95%} 76.9–83.2], for DTP (diphtheria–tetanus–pertussis) 510 (80%) [Cl_{95%} 76.7–83.1], for HB 429 (67.4%) [Cl_{95%} 63.6–70.9], monovalent for measles 327 (51.3%) [Cl_{95%} 47.4–55.3], for MMR (measles–mumps–rubella) 116 (18.2%) [Cl_{95%} 15.3–21.4], and for

Table 1 Demographic characteristics of the children (n = 637)

Area of origin	Countries	No. and (%) by country	No. (%) by area [CI _{95%}]	No. (%) setting in orphanage	Median time of setting (months)	No. (%) of malnourished (NI ≤ 89%)
Asia	China India Nepal	291 (45.68) 132 (20.72) 16 (2.51)	439 (69.1) [65.3–72.5]	244 (83.8) 132 (100) 16 (100)	13 24 9	208 (71.5) 116 (87.9) 8 (50)
Eastern Europe	Russia Ukraine Bulgaria Rumania Hungary	71 (11.15) 31 (4.87) 8 (1.26) 2 (0.31) 1 (0.16)	113 (17.8) [14.8–20.7]	110 (97.3)	22	95 (84)
Latin America	Colombia Bolivia Haiti Mexico Ecuador Peru Brazil El Salvador Honduras Panama	19 (2.98) 16 (2.51) 6 (0.94) 4 (0.63) 2 (0.31) 2 (0.31) 1 (0.16) 1 (0.16) 1 (0.16) 1 (0.16)	53 (8.3) [6.3–10.7]	38 (71.7)	17	36 (68)
Africa	Ethiopia Mozambique Morocco Burkina-Faso Ghana Madagascar	24(3.77) 3 (0.47) 2 (0.31) 1 (0.16) 1 (0.16) 1 (0.16)	32 (4.8) [3.5–7]	30 (93.7)	9	23 (72)

no. = number of children; % = percentage of children; NI = McLarenĭs nutritional index.

BCG vaccine 507 (79.6%) [Cl_{95%} 76.2–82.7]. There was a perceptible BCG scar in 520 children (81.6%).

4.3. Nutritional and immunological status

McLaren's nutritional index (NI) was calculated for all of the children: 151 (23.7%) had a normal nutritional status (NI \geq 90%), 382 (60%) were considered as suffering moderate malnutrition (NI 70–89%) and 16% were severely malnourished (NI \leq 69%).

Serum immunoglobulins and lymphocyte subsets were determined to evaluate immunological status. The result of IgG was normal in 81%, of IgM in 86%, and IgA in 92%; 93% had normal values of CD4. For all of the children with abnormal results, the next check-up showed normalization of the parameters.

4.4. Vaccine serology (Table 3)

The results of vaccine serology showed protective antibody titres of 89% for poliovirus 1, 96% for poliovirus 2 and 90% for poliovirus 3. Eighty-six percent of the children were fully protected against the three polioviruses. For 16 children (2.5%), the serology was negative for poliovirus 1, 2 and 3, despite the fact that 7 of them had valid vaccine records with updated doses of poliovirus vaccine; 12 out

Table 2Characteristics of vaccine records related to areas of origin

Origin	Validity of vac	ccine records no.	. and (%)
	Valid	Non-valid	No record
China (n = 291)	247 (84.9%)	31 (10.7%)	13 (4.4%)
India (n = 132)	82 (62.1%)	31 (23.5%)	19 (14.4%)
Nepal (n = 16)	2(12.5%)	1 (6.3%)	13 (81.2%)
East Europe ($n = 113$)	93 (82.3%)	12 (10.6%)	8 (7.1%)
Haiti (n = 6)	0 (0%)	1 (16.7%)	5 (83.3%)
Latin America $(n = 47)$	34(72.3%)	8 (17.1%)	5 (10.6%)
Ethiopia $(n = 24)$	1 (4.2%)	2 (8.4%)	21 (87.4%)
Africa (n=8)	7 (87.5%)	0 (0%)	1 (12.5%)

of 16 came from China. For tetanus, 92% of the children showed protective titres and 76% for diphtheria. In the case of MMR, 79% of the children had positive antibodies for measles, 30% for mumps and 38% for rubella. There were no significant differences in the rate of protective antibody titres in children younger than 12 months of age and those 12 months or older, except for measles, mumps and rubella with higher rates of protection in children 12 or more months old.

We obtained HB serology in all of the children, but 35 of them not only had HB surface antibodies but also HB core antibodies. In these cases, we could not ascertain if the presence of HBs-Ab was related to vaccine or to natural infection, so, to avoid bias, we decided to exclude this subgroup from the analysis of HB-vaccine protection. In the remaining 602 children, 457 (76%) were fully protected.

4.5. Relationship between vaccine serology and independent variables: bivariate and multivariate analysis (Table 4)

4.5.1. Country of origin

There was a significant statistical difference in vaccine protection for all of the studied antigens depending on the geographic

Table 3Results of vaccine serology

	% of protected children [CI $_{95\%}$]
Poliovirus 1	89 [86.1-91.1]
Poliovirus 2	96 [94.5-97.7]
Poliovirus 3	90 [87.6-92.4]
Tetanus	92 [89.5–94.1]
Diphtheria	76 [72.3–79.2]
Measles	79 [75.6–82.0]
Mumps	30 [26.1–33.2]
Rubella	38 [34.1-41.6]
Hepatitis B	76 [72.5–79.3]

Cut-off titres considered to be protective: poliovirus >1: 2; tetanus and diphtheria >0.1 IU/mL; measles >150 mIU/mL; mumps >1: 231; rubella >4 IU/mL; hepatitis B > 10 IU/L.

zone of origin (p<0.001). This significance was obtained both by bivariate and multivariate analysis. In fact, multivariate analysis showed that the only independent factor associated with serological protection against all of the vaccine antigens was the area of origin of the children: children coming from Eastern Europe showed the best rates of protection, followed by India, Latin-America (except Haiti), China, Nepal, Africa and Haiti (Table 5).

4.5.2. Type of setting previous to adoption

There was no relationship found between type of setting (orphanage/foster care) and serological protection (p > 0.05) neither by univariate nor multivariate analysis.

4.5.3. Age at adoption and period of time institutionalized

In univariate analysis, children adequately protected against poliovirus, measles, mumps and rubella were significantly (p < 0.001) older than those not protected. For the remaining antigens, the protected children were younger than the non-protected ones. The time of institutionalization had been longer for the protected children, with statistical significance (p < 0.05) in the cases of polio 1, polio 3, measles, mumps and rubella. In multivariate analysis, the difference was found only for measles and rubella.

4.5.4. Immunization records

Seroprotection rates were significantly lower in children without immunization cards than in those who had vaccine records, specially for tetanus (p 0.001), diphtheria (p 0.004) and hepatitis B (p < 0.001). For the rest of the antigens, differences were not so evident, but in all of the cases the protection rate was better in those with vaccine cards. In children with immunization records. there was a poor agreement between the number of doses for each antigen (completeness for age) recorded in the immunization card and serological results (k statistics approached 0.0 for all antigens except for mumps, rubella, and hepatitis B that were 0.411, 0.461, and 0.452, respectively). However, in relation to all of the antigens excepting poliovirus, children whose immunization records referred to the number of doses being up-to-date for their age were better protected (p < 0.05) than those for whom they did not. In multivariate analysis, these differences only remained for measles, mumps, rubella and HB.

4.5.5. Validity of immunization records

In multivariate analysis there were no statistical differences (except for poliovirus 1 and 2 and HB) in the serological protection of the children whose immunization records were considered valid according to the AAP [13] and those whose records were not valid or did not have any immunization record.

4.5.6. Nutritional and immunological status

There were not any differences in the vaccine protection of the children due to either their nutritional status (p > 0.05) or the results of the immunoglobulin and CD4 subsets.

5. Discussion

The continuing increase of international adoption is a new challenge for paediatricians. One of the main issues in the initial assessment of these children is their immunization status. We have presented the results of vaccine serology obtained in 637 internationally adopted children. We consider that the immunization status in these children represents the general immunization status of all the adopted children in Spain. Our hospital depends on the Spanish Health Public Services and the check-up in adopted children is offered cost free. Moreover, adoptive families in Spain are

 Table 4

 Relationship between vaccine serology and analyzed independent variables (bivariate and multivariate analysis)

	Independent variables	dent var	riables														
	Bivariate ^{a, b}	a,b							Multivari	Multivariate ^{a,b,c,d}							
	P1	1 P2 P3	P3 1		D	M Mu	R	HB	P1	P2	P3	T	D	M Mu		R I	HB
Area of origin	<0.001	0.001 0.004 0.005		0.001	< 0.001	> 10000		<0.001	0.008	0.032	0.005	0.003	< 0.001	< 0.001	< 0.001	< 0.001 < 0.001 < 0.001 < 0.001 < 0.001	<0.001
Setting in orphanage	0.040	0.040 0.296 0.077		> 0.999	0.433	0.755		0.057									
Time of institutionalization	<0.001 0.742	0.742	0.039	0.157	0.270	0.157 0.270 < 0.001 < 0.001	<0.001	0.239						0.003		0.001	
Record with updated number of doses for age	0.525 0.102		0.309	0.007	0.016	< 0.001 <		<0.001						< 0.001	< 0.001		<0.001
Valid record	980'0	0.086 0.007 0.168		0.083	0.277	0.325 <		<0.001	0.023	0.012							0.018
Nutritional index	0.208	0.208 0.220	0.642	0.300	0.475	0.253 0.074	0.005	0.442									

P1: poliovirus 1; P2: poliovirus 2; P3: poliovirus 3; T: tetanus; D: diphtheria; M: measles; Mu: mumps; R: rubella; HB: hepatitis B.

³ Table shows the relationship between protective titers for each one of vaccine antigens and independent variables, using bivariant and multivariate analysis. In multivariate analysis only variables with p < 0.20 in bivariate

b Presence of protective titers.

were included.

 c In multivariate analysis, only statistically significant results (p < 0.05) are showed.

In multivariate analysis, spaces in blank are those of variables which did not show statistical significance after logistic regression or those which have not been included because of p>0.20 in bivariant analysis.

mostly middle class families and they are informed by the Collaborator Agencies for International Adoption about the importance of ruling out any health problems and of assessing the immunization status in adopted children as soon as they arrive in Spain. For this reasons we think that in the adoptive families of the children included in our study there were no socioeconomic restrictions that could have constituted a selection bias. Our study shows a high rate of seroprotection for most immune-preventable diseases in adopted children—89%: poliovirus 1; 96%: poliovirus 2; 90%: poliovirus 3; 92%: tetanus; 76%: diphtheria; 79%: measles; 76%: HB. However, the rate of seroprotection for mumps (30%) and rubella (38%) were much lower.

There have been very few reports published about the vaccine protection levels of children adopted from abroad [7-12], and they have had conflicting results. In the studies carried out between 1998 and 2001 [7–11], the rate of immune protection for polioviruses varied between 58% and 94%, and against tetanus and diphtheria between 38% and 94%. In a report published in 2006, Viviano et al. [12] found protection against poliovirus 1 in 82.8% of the cases, poliovirus 2 in 98.6%, poliovirus 3 in 62.8%, tetanus in 91.4% and diphtheria in 95.7%. In the case of MMR, the only data reported was by Miller et al. [10] and Viviano et al. [12]; Miller found protection against measles—90%, mumps—66% and rubella—79%; Viviano reported positive antibodies of 61%-measles, 51%-mumps and 66%—rubella. The HB percentages of protection were around 65% in all of the studies. In these reports, none of the authors found a relationship between vaccine protection and variables such as the country of origin, age, nutritional status or the setting where children had been before adoption. All these authors concluded that internationally adopted children should be tested for levels of antibodies against immune-preventable diseases, regardless of their vaccine records, at least until there were more exhaustive studies.

An intriguing finding in our study is that the percentage of children adequately protected against diphtheria has always been lower than the percent protected against tetanus, in spite of the fact that both vaccines are delivered together. Discrepancy between the rate of antibodies against tetanus and diphtheria has been shown in adult populations. In most of these studies the protection rate for diphtheria is lower than for tetanus, these discrepancies being attributed to booster doses of tetanus toxoid recommended in some adult vaccination schedules [20,26,27]. These findings, however, have not been confirmed in children although a study carried out in Thailand has demonstrated that, 7 years after the vaccination, the percentage of children seroprotected against diphtheria is 9% lower than against tetanus [28].

The difference between previously published data and our study is more evident if we analyze the periods of time of arrival of the children: the vaccine protection levels of children who arrived in the 1990s were lower than those of children who have arrived after 2000. One possible explanation is that there has been an improvement in both financial resources and vaccine policy during the last few years in the orphanages. Another reason may be the different laboratory tests used. It is also important to bear in mind that most of the published articles investigated vaccine serology exclusively in those children who had supposedly received ≥ 3 doses of each vaccine. However, we performed serological tests for vaccinepreventable diseases on all of the children involved, regardless of their vaccine records. So, we also included children with ≤2 doses and children who did not have any vaccine record and who could not have received any vaccine doses. Even with these considerations, our results show a higher rate of protection than previously

In this study, we have analyzed different variables which could be related with vaccine protection, trying to identify the possible existence of some clearly predictive factor for immune protection in this group of children. After bivariate and multivariate analysis, we have been able to conclude that, in our study, the only independent factor associated with vaccine protection against all of the antigens has been the country of origin. In fact, the main result of this study is that the country of origin can predict vaccine immune-protection in internationally adopted children. The best global protection, similar to Spanish children [20,29] (except for MMR), was found in children coming from Eastern Europe. Then, in descending order, there followed: India, Latin-America, and China. Low protection rates were found in children coming from Africa, Nepal and Haiti.

The results of protection against the antigens of MMR were of particular interest. The high percentage of children susceptible to mumps (70%) and rubella (62%), and also a considerably high percentage to measles (21%), could be very important in the development of outbreaks of these diseases due to the addition of such populations to other non-immune groups. In fact, during recent years, outbreaks of measles, mumps and rubella have been reported in Spain [30,31] and in other countries [32,33], mainly with patients from abroad.

With regard to vaccine records, comparing those that we studied with those of previous reports [12,15,16], we find a very high proportion of children with vaccine documentation, valid documents of vaccination, and completeness and correctness of schedule: 86.7% of the children arrived with vaccine documentation and of these, 73.2% were considered as valid according to the criteria of the AAP [13] and the ACIP [17], and 13.5% were non-valid, mainly because of the lack of signature or seal of the vaccine provider. These figures varied depending on the area of origin; most of the children coming from Eastern Europe, China, India and Latin-America had valid vaccine records. We did not find differences in the validity of vaccine records between children from orphanages and those from foster care, as was also the case with other authors [10,12,15,16].

An important fact is how the immunization records should influence the immunization policy. Ours results show that adopted children who do not have card immunization have a high risk of being susceptible to immune-preventable diseases and consequently they should receive a complete immunization schedule according to their age (Table 6). The existence of an immunization card, no matter if it is considered valid or non-valid, implies a better global protection but do not allow to establish a priori immune protection against each vaccine antigen. In this setting, we propose several different immunization actions or the administration of booster doses (see "Final Recommendations") depending on the country of origin that, in turn, determines the rates of seroprotection for each antigen (Table 5). A substantial proportion of our children, independently of the country they come from, were susceptible to measles, mumps and rubella. So, we recommend at least a dose of MMR vaccine in all adopted children. For the rest of vaccine antigens, the immunization of the children should be based on other factors mainly the country of origin and the age of the child (Table 6). Finally, children from Africa, Haiti and Nepal, who have very low rates of seroprotection (Table 5) should be completely vaccinated according to their age and the vaccination schedule of the adoptive country (Table 6).

From a practical point of view, we think that, with the only exception of hepatitis B, laboratory tests to establish the status of seroprotection for each antigen are not indicated. Some of these tests are not routinely performed in most laboratories and they are unlikely to be cost-effective.

Another interesting issue is that of the completion of vaccination in accordance with age. Our results show that, according to vaccine records, 80% of the children had received the complete series of vaccines for polio, tetanus and diphtheria, 67% for HB, 50% for monovalent measles and only 18% for MMR, with differences among the countries of origin. These data are similar to those

rcentages of children adequately protected against vaccine antigens in relation to areas of origin

Origin	P1	P2	P3	Т	D	M	Mu	R	HB
Eastern Europe $(n = 113)$	95.5	99.1	93.8	86	91	71.7	43.4	64.6	83.2
India $(n = 132)$	98.4	99.2	98.4	93.4	7.77	86.4	50.8	56.8	62.9
Latin America $(n = 47)$	87	100	82.6	93.2	75	70.2	99	80.9	76.6
China $(n = 291)$	82	94.8	87.4	92	76.4	82.5	6.2	13.1	85.5
Ne pal $(n = 16)$	93.3	100	93.3	71.4	35.7	81.3	62.5	62.5	18.8
Ethiopia $(n = 24)$	86.4	6.06	86.4	73.9	39.1	20	37.5	20.8	4.2
Rest of Africa $(n = 8)$	75	87.5	87.5	100	37.5	62.5	12.5	12.5	20
Haiti $(n=6)$	20	20	20	20	25	66.7	66.7	16.7	16.7

P1: poliovirus 1; P2: poliovirus 2; P3: poliovirus 3; T: tetanus; D: diphtheria; M: measles; Mu: mumps; R: rubella; HB: hepatitis B.

Table 6Recommended immunization schedule

Area of origin	Age	Vaccines to be administered
Eastern Europe	<15 months >15 months	– 1 dose of MMR
India	<15 months >15 months	1 dose of DTPa +1 dose of MMR
Latin America	<15 months >15 months	1 dose of DTPa and IPV +1 dose of MMR
China	<15 months >15 months	1 dose of DTPa and IPV +1 dose of MMR
Africa, Nepal and Haiti	<15 months >15 months	Complete vaccination schedule

MMR: measles-mumps-rubella vaccine; DTPa: diphtheria-tetanus-pertussis acellular vaccine; IPV: inactivated poliovirus vaccine.

of Viviano et al. [12], but very different from the results of other reports, which showed up-to-date vaccination for age in 9–28% of the children [15,16]. It is important to consider that, in these studies, monovalent measles vaccine administered before 12 months of age was considered to be an invalid dose, the same as poliovirus vaccine received at birth. Anyway, the differences between the results are quite apparent, and, although it is very difficult to ascertain the reasons for this, it is possible that they are related with the different time periods of the studies. If this is the case, our results could point to an improvement in the administration of vaccines in the settings where the children stayed before their adoption.

6. Final recommendations for the immunization of foreign adopted children

- Children without a vaccine record need to undergo a complete schedule in accordance with their age and the general recommendations on immunization from the adoptive country.
- (2) Children with vaccine records (valid or non-valid) (Table 6):
 - (a) Children coming from Eastern Europe: Vaccination schedule should be continued according to their age and the schedule of the adoptive country. All those children ≥15 months should receive one dose of MMR vaccine. Serologic testing for hepatitis B should be performed and susceptible children should receive a complete series (three doses) of hepatitis B vaccine.
 - (b) Children coming from India: They should receive one dose of DTPa/DTPw vaccine. Vaccination schedule should be continued according to their age and the schedule of the adoptive country. All those children ≥15 months should receive one dose of MMR vaccine. Serologic testing for hepatitis B should be performed and susceptible children should receive a complete series (three doses) of hepatitis B vaccine.
 - (c) Children coming from Latin American and China: They should receive one dose of IPV and DTPa/DTPw vaccine. All those children ≥15 months should receive one dose of MMR vaccine. Vaccination schedule should be continued according to their age. Serologic testing for hepatitis B should be performed and susceptible children should receive a complete series (three doses) of hepatitis B vaccine.
 - (d) Children from Africa, Nepal and Haiti: They should receive a complete primary series of IPV and DTPa/DTPw vaccines. All those children ≥ 15 months should receive one dose of MMR vaccine. Vaccination schedule should be continued according to their age. A complete three-dose series of hepatitis B vaccine should be administered.

This study has several limitations. First, the presence of antibodies against vaccine-preventable diseases in some of our children could be due to maternal transference of antibodies more than the immunization, especially in relation with measles-mumps-rubella. This effect would be more significant in infants younger than 15 months. Mean age of our patients was 27 months, an age in which maternal antibodies have disappeared from infant's serum. However, there were 240 children younger than 15 months. In any case, our recommendation is to vaccinate with a dose of MMR to all children older than 15 months. Another potential bias is that in some children the presence of antibodies to measles, mumps and rubella could reflect a past infection by wild virus more than vaccine induced immunity. This fact, however, would not affect the final recommendation about vaccination (administration of one dose of MMR vaccine to all adopted children older than 15 months of age) since these patients would also be protected.

In our opinion, the high number of patients from China, India, and Eastern Europe make our recommendations applicable for adopted children from these countries. The validity of conclusions about some other countries may be questionable due to the low number of patients. However these cases should be taken into account since they provide some useful information when deciding how to vaccinate them.

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References

- [1] Johnson DE. International adoption: what is fact, what is fiction, and what is the future? Pediatr Clin North Am 2005;52:1221–46.
- [2] Miller LC. Caring for internationally adopted children. N Engl J Med 1999;341:1539–40.
- [3] Hostetter MK, Iverson S, Dole K, Johnson DE. Unsuspected infectious diseases and other medical diagnoses in the evaluation of internationally adopted children. Pediatrics 1989;83:559–64.
- [4] Aronson J. Medical evaluation and infectious considerations on arrival. Pediatr Ann 2000;29:218–23.
- [5] Barnett ED. Immunizations and infectious disease screening for internationally adopted children. Pediatr Clin North Am 2005;52:1287–309.
- [6] Murray TS, Groth ME, Weitzman C, Cappello M. Epidemiology and management of infectious diseases in international adoptees. Clin Microbiol Rev 2005:18:510–20.
- [7] Hostetter MK, Johnson D. Immunization status of adoptees from China, Russia and Eastern Europe. Pediatr Res 1998;43:147 (Abstract no. 851).
- [8] Miller LC. Internationally adopted children—immunization status. Pediatrics 1999;103:1078.
- [9] Staat MA, Daniels D. Immunization verification in internationally adopted children. Pediatr Res 2001;49:468 (Abstract no. 2680).

- [10] Miller LC, Comfort K, Kely N. Immunization status of internationally adopted children. Pediatrics 2001;108:1050–1.
- [11] Schulpen TW, van Seventer AH, Rümke HC, van Loon AM. Immunization status of children adopted from China. Lancet 2001;358:2131–2.
- [12] Viviano E, Cataldo F, Accomando S, Firenze A, Valenti RM, Romano N. Immunization status of internationally adopted children in Italy. Vaccine 2006;24:4138–43.
- [13] American Academy of Pediatrics. Medical evaluation of internationally adopted children for infectious diseases. In: Pickering LK, editor. Red book: 2003 report of the Committee on Infectious Diseases, 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003, p. 173–80.
- [14] Saiman L, Aronson J, Zhou J, Gómez-Duarte C, Gabriel PS, Alonso M, et al. Prevalence of infectious diseases among internationally adopted children. Pediatrics 2001;108:608–12.
- [15] Schulte JM, Maloney S, Aronson J, San Gabriel P, Zhou J, Saiman L. Evaluating acceptability and completeness of overseas immunization records of internationally adopted children. Pediatrics 2002:109:E22.
- [16] Miller L, Chan W, Comfort K, Tirella L. Health of children adopted from Guatemala: comparison of orphanage and foster care. Pediatrics 2005:115:e710-7.
- [17] Kroger AT, Atkinson WL, Marcuse EK, Pickering LK, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55:1–48.
- [18] McLaren DS, Read WW. Classification of nutritional status in early childhood. Lancet 1972:2:146–8.
- [19] Miller LC. International adoption: infectious diseases issues. Clin Infect Dis 2005;40:286–93.
- [20] Pachón I, Amela C, de Ory F. Age specific seroprevalence of poliomyelitis, diphtheria and tetanus antibodies in Spain. Epidemiol Infect 2002;129:535–41.
- [21] WHO manual for the serological investigation of polio. WHO/EPI/GEN 97.01 Geneva, WHO; 1997.
- [22] Galazka AM. The immunological basis for immunization series. Module 2: Diphtheria. Global Programme for Vaccines and Immunization. Expanded Programme on Immunization. World Health Organization, Geneva. WHO/EPI/GEN/93.12.
- [23] Borrow R, Balmer P, Roper MH. The immunological basis for immunization series. Module 3: Tetanus. Update 2006. Immunization, Vaccines and Biologicals. World Health Organization, Geneva; 2007.
- [24] Cutts FT. The immunological basis for immunization series. Module 7: Measles. Global Programme for Vaccines and Immunization. Expanded Programme on Immunization. World Health Organization, Geneva. WHO/EPI/GEN/93.17.
- [25] Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 1989. pp. 86–88.
- [26] Aue A, Hennig H, Krüger S, Closius B, Kirchner H, Seyfarth M. Immunity against diphtheria and tetanus in German blood donors. Med Microbiol Immunol 2003;192:93–7.
- [27] Crossley K, Irvine P, Warren JB, Lee BK, Mead K. Tetanus and diphtheria immunity in urban Minnesota adults. JAMA 1979;242:2298–300.
- [28] Poovorawa Y, Hutagalung Y, Chongsrisawat V, Thaemboonlers A, Lefevre I. Longterm antibody persistence in children primed and boosted with a DTPw-vaccine at 2, 4, 6, 18 months of age. Vaccine 2008;26:1535–41.
- [29] Amela C, Pachón I, de Ory F. Evaluation of the measles, mumps and rubella immunisation programme in Spain by using a sero-epidemiological survey. Eur J Epidemiol 2003;18:71–9.
- [30] Montes M, Cilla G, Artieda J, Vicente D, Basterrechea M. Mumps outbreak in vaccinated children in Gipuzkoa, Spain. Epidemiol Infect 2002;129:551– 6.
- [31] Perucha M, Ramalle-Gómara E, Lezaun ME, Blanco A, Quiñones C, Blasco M, et al. A measles outbreak in children under 15 months of age in La Rioja, Spain, 2005–2006. Euro Surveill 2006;11:267–70.
- [32] Rooney JA, Milton DJ, Hackler RL, Harris JH, Reynolds D, Tanner M, et al. The largest outbreak of measles in the United States during 1999: imported measles and pockets of susceptibility. J Infect Dis 2004;189:S78–80.
- [33] Centers for Disease Control and Prevention (CDC). Measles outbreak associated with an imported case in an infant Alabama, 2002. MMWR Morb Mortal Wkly Rep 2004; 53:30–3.