Tetanus Immunity as a Surrogate for Past Diphtheria-Tetanus-Pertussis Immunization in Migrant Children

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Background: Data on vaccination coverage in recently arrived refugee children are essential to formulate catch-up recommendations. "Overimmunizing" is costly and associated with risks of hyperimmunization, whereas assuming up-to-date immunizations may be misleading.

Methods: We retrospectively collected data from 92 migrant children referred to our hospital between January 2009 and May 2010.

Results: According to our guidelines, 68 (73.9%) children without evidence of up-to-date immunizations received a booster dose of an age-appropriate tetanus-containing vaccine. As a surrogate for diphtheria-tetanus-pertussis-poliomyelitis immunity, tetanus antibodies were measured by enzyme-linked immunosorbent assay 1 month later in 55 of 68 (80.8%) children 6 months to 16 years of age (median, 7 years) from 23 countries. All but 2 children (3.6%) had reached high antibody titers (>1.0 IU/mL) and required no further booster. Unnecessary additional tetanus immunizations thus were avoided in 53 of 55 (96.4%) patients.

Conclusion: Assessing antitetanus antibody responses in migrant children allows individual vaccination schedules and avoids the risks of hyperimmunization.

Key Words: children, immigration, tetanus immunization, antibody responses, hyperimmunization, vaccination

(*Pediatr Infect Dis J* 2013;32: 274–277)

Tetanus remains a major cause of vaccine-preventable morbidity and mortality despite the dramatic reduction of disease since the implementation of World Health Organization immunization programs and introduction of universal vaccination. Globally, there are 1 million cases yearly worldwide, with a mortality rate up to 30–50%, occurring mainly in developing countries.[1] In developed countries, immigrants from economically challenged countries, political refugees and adopted children represent a particularly vulnerable population because of unknown, incomplete or missed immunization.[2–7] Data on tetanus vaccination coverage in newly arrived immigrant children in Europe are missing. There is currently no universal guideline on how to catch-up immunization in migrant children with no available or reliable vaccination records. Theoretically, several possibilities exist: serology testing at the first visit; serology testing 1 month after a "booster" vaccination; or a full primary immunization (3 doses) with age-appropriate vaccines, regardless of previous vaccination.[8] Unnecessary vaccination of children is associated with an increased risk of severe adverse reactions, such as hyperimmunization, which includes significant and painful local swelling, erythema or fever. In contrast, assuming an up-to-date vaccination history may be misleading and may result in vulnerability to vaccine preventable diseases. This study reports the outcome of our strategy in which we measured antitetanus antibody responses as a surrogate for diphtheria-tetanus-pertussis-poliomyelitis immunization in immigrant children after a single vaccination.

METHODS

Demographic and clinical data from recently arrived immigrant children were analyzed retrospectively from hospital records between January 2009 and May 2010. The Children's Hospital of Geneva, part of the University Hospitals of Geneva, is the only center in our region that provides health care to all immigrant children on arrival to our area, with a focus on their health, developmental and vaccination status. Self-reported vaccination status and available medical records for immunization were reviewed when available.

Children with unavailable or incomplete diphtheria-tetanus-pertussis-poliomyelitis vaccination records received a single dose of an age-appropriate combination vaccine according to the Swiss recommendation to provide catch-up pertussis immunization up to the age of 15 years.[9] Children younger than 8 years received Infanrix-hexa (DTPa-IPV-HBV/Hib) or Infanrix (DTPa-IPV/Hib; both from GlaxoSmithKline, Philadelphia, PA) if their hepatitis B immunization status was up-to-date. For those 8 years of age or older, combination vaccines including tetanus toxoid, inactivated poliomyelitis viruses and a reduced dose of diphtheria toxoid without (Revaxis; Sanofi Pasteur MSD, Lyon, France) or with (Boostrix-polio; GlaxoSmithKline) pertussis antigens were administered.

Vaccine adverse events were solicited at the next visit. Antibodies (IgG) against tetanus were measured 1 month after booster vaccination by enzyme-linked immunosorbent assays in the Vaccinology Laboratory of the University Hospitals of Geneva using standardized methods. Antitetanus IgG values ≥0.1 IU/mL and ≥1.0 IU/mL were considered as correlating with short-term and long-term protection, respectively.

Following Swiss recommendations,[9] missing catch-up immunizations were recommended for each patient depending on age and antibody titers. This included 2 additional boosters for children with antitetanus toxoid (TT) antibodies <0.5 IU/mL and a single additional booster for those with anti-TT antibodies between 0.5 and <1.0 IU/mL.[9]

RESULTS

Study Population

A total of 92 patients were evaluated. The children originated from 23 countries, with most coming from Eastern Europe

Accepted for publication September 14, 2012.

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The authors have no funding or conflicts of interest to disclose.

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ISSN: 0891-3668/13/3203-0274
DOI: 10.1097/INF.0b013e3182748f0b

(39%) and sub-Saharan Africa (26%). On arrival to Switzerland, they were between 6 months and 16 years old (median, 7 years). No child in this cohort was HIV-positive.

Self-reported Vaccination Status and Vaccination Records

Only 4% (4 patients) had available vaccination records. Based on parental recall, 27% (25 patients; median age, 3.5 years) were considered as up-to-date for diphtheria-tetanus-pertussis (DTP) vaccination. A significant proportion of parents (of 18 children; 19.5%) reported no or incomplete previous vaccinations in their country of origin. Almost half of the parents (of 45 children; 48%) recalled at least one DTP injection in their children but did not know if the children were up-to-date on immunizations.

Booster Immunization

Tetanus-containing vaccines were administered to 68 children, including 63 children with unknown or incomplete previous immunization. Five children up to date with their DTP immunizations received an age-based, routine, tetanus-containing booster. At the 1-month follow-up visit, severe inflammatory local or systemic adverse events were not spontaneously reported, indicating the good tolerance of this single booster.

Vaccine Responses to Booster Vaccination

Antibody responses after a single tetanus-containing vaccine were measured in 55 of 63 (87.3%) patients (younger than 2 years: 2; 2–5 years: 12; 5–10 years: 19; 10–16 years: 22) with unknown or incomplete previous immunization. All had reached anti-TT titers >0.1 IU/mL. We divided the patients in 3 groups: (1) patients with low antibody titers (<1.0 IU/mL) requiring further tetanus-containing boosters to ensure long-term protection; (2) patients with normal postbooster titers (1.0–10 IU/mL), to whom the next booster was recommended according to the normal Swiss immunization schedule;[9] and (3) patients with high antibody titers (defined as >10 IU/mL), for whom the next recommended vaccination was postponed by 5 to 20 years depending on their age and antibody titers. Only 2 (3.6%) patients (a 5-year-old boy from Turkey and a 9-year-old girl from Kosovo) had postbooster anti-TT titers <1.0 IU/mL, indicating incomplete immunity. Thus, a single booster was sufficient for 53 (96.4%) patients to reach high (>1.0 IU/mL) antibody levels (Table 1). Sixty-three percent of the patients (n = 35) reached anti-TT titers >10 IU/mL, including 6 with very high antibody titers (≥30 IU/mL; Table 1), suggesting that they would not have required the administered vaccine.

Relationship Between Reported Vaccination Status and Immunity

We found no relationship between reported data through parental recall and seroresponse. Eight patients had antibody titers >10 IU/mL and 1 had antibody titers >30 IU/mL, although they were reported as being never or not fully vaccinated before their arrival.

DISCUSSION

Our study assessed the serological protection against tetanus in immigrant children. As in studies of adult refugees,[10,11] a large proportion of immigrant children did not have vaccination records on arrival. Whereas only approximately half of the patients' parents recalled their children having received at least 1 dose of tetanus vaccine, >96% of children responded to a single vaccination with protective levels and therefore required no further catch-up immunization. This represents a much higher protection rate than expected from the literature, in which only 35–87% of adopted children or immigrant patients had protective tetanus antibody levels.[4,12] This possibly could be explained by a high proportion of children coming from Eastern Europe with, until recently, high vaccination coverage and by the absence of children arriving from China, who seem to be a particularly vulnerable population.[12] The effect of the World Health Organization/ United Nations Children's Fund campaigns in sub-Saharan Africa also may have played a role, but because of the heterogeneity of our population we could not analyze each country separately. In addition, most children arrived in good clinical condition, without malnutrition or HIV infection, which may account for their good past and present immune capacity.

Serotesting after a single vaccination identified sufficiently immunized children and avoided many unnecessary additional vaccinations. It identified the few children who most likely were never vaccinated previously or who had not generated a sufficient pool of memory B cells; their postboosting antibody levels remained <1.0 IU/mL. Although this was not formally tested here, seroresponses to a single (possibly "booster") vaccination is likely a better predictor of previous tetanus vaccination/baseline immunity than baseline antibody measurements; postimmunization responses reflect the persistence and "boostability" of specific memory B cells and may persist long after the disappearance of antibodies.[13]

The results of our study should discourage from starting complete vaccination schedules without serological testing in immigrant children, because most of the children, even when they claim that they were never vaccinated, did not need a complete catch-up. It also may expose them to the risk of hyperimmunization. Although minor adverse reactions to vaccination were not systematically recorded in the patients' files, no severe adverse reaction was reported, even for our patients with very high antibody responses. This suggests that their baseline antitetanus titers were low at time of boosting, avoiding the generation of inflammatory immune complexes. Although this cannot be proven, it is likely that the high or very high titers elicited after the first booster would have generated more severe adverse events if an additional immunizations had been empirically administered.

This study reports our results for tetanus immunity; however, immigrant children often have poor immunization coverage for other vaccine-preventable diseases as well.[14] Recently, Paxton et al[14] confirmed that almost all pediatric immigrants in their institution coming from East Africa had unknown or incomplete vaccination status, and only 15% of children presented with serological immunity against tetanus, hepatitis B, diphtheria, rubella or measles. Furthermore, several authors also demonstrated that even after resettlement, patients were not vaccinated appropriately and had many missed opportunities, ie, medical visits, for vaccination catch-up.[5,14] Even today, immigrant children remain a vulnerable group for health-related issues, despite available recommendations.[11] In our institution, we design vaccination schedules based on the age of the patient, vaccination records (if available), and risk factors (Table 2). We usually administer a maximum of 3 vaccines simultaneously for comfort reasons, and inject live attenuated vaccines either simultaneously or separated by 4 weeks, as recommended.[9] The catch-up schedule is initiated at the first visit and completed as rapidly as possible thereafter (2–6 months) to protect children as quickly as possible, and before their residence status is decided. All parents receive a copy of the vaccination records, and the new primary care physician also receives a copy in case the children become residents. Our study was not designed as a cost-analysis study. However, the costs of measuring antibody titers, which vary from country to country, were much lower than the costs of the 2 additional tetanus-containing combination vaccines. Furthermore, we used a skin anesthetizing cream to significantly reduce the

TABLE 1. Antibody Response After Tetanus Vaccination (Booster Dose) and Protection Against Tetanus in 55 Migrant Children

	Tetanus Antibody Titers (IU/mL)					Immunity to Tetanus According to Antibody Titers						
						Low Titers (<1 IU/mL)		Normal Titers (1 – <10 IU/mL)		High Titers (≥10 IU/mL)		
Age Groups (yr)	<0.1	≥0.1 – <1	≥1 – <10	≥10 – 30	≥30	n	GMT (IU/mL)	n	GMT (IU/mL)	n	GMT (IU/mL)	Total
≥0.5 and <2	0	0	1 (50%)	1 (50%)	0	0	—	1	5.9	1	11	2
≥2 and <5	0	0	3 (25%)	6 (50%)	3 (25%)	0	—	3	5.7	9	21.6	12
≥5 and <10	0	2 (10.5%)	6 (31.5%)	11 (58%)	0	2	0.25	6	7.0	11	15.5	19
≥10 and ≤16	0	0	8 (36.4%)	11 (50%)	3 (13.6%)	0	—	8	5.5	14	18.7	22
Total	0	2 (3.6%)	18 (32.7%)	29 (52.7%)	6 (10.9%)	2 (3.6%)		18 (32.7%)		35 (63.6%)		55

Number of patients (and % per age group) according to age groups (years) and tetanus antibody titers (IU/mL) 1 month after vaccination.
GMT indicates geometrical mean titers (IU/mL).

discomfort of phlebotomy, although this method has shown little efficacy for decreasing the discomfort of intradermal vaccination.

Our study has some limitations. First, we did not have enough patients to determine predictive factors for vaccine responses according to country of origin (and their vaccination schedules), age or gender. Larger studies would be needed to identify such subgroups and to define vaccination strategies based on demographics. Furthermore, because many of our patients came from Eastern Europe, it is possible that our conclusions may not apply to children coming from Asia or Latin America. Second, there is a small percentage of children who respond suboptimally even to tetanus vaccination. Therefore, it is possible that the 2 children with low antibody titers were "poor responders" rather than undervaccinated children. However, low responders do benefit from additional boosters, making this difference more academic than clinically relevant. Third, antibody titers were not assessed before booster vaccination, precluding the identification of the proportion of children in whom even the single booster could have been avoided. Given our national guidelines to provide catch-up immunization as soon as possible to migrant children who may not benefit from a prolonged medical follow-up, this would have required a clinical trial study design. Although such a study is, in theory, feasible, it was deemed problematic in this vulnerable population that lacked familiarity with research studies, had communication issues, had limited interaction time and other factors. Finally, we have opted for the determination of antitetanus antibodies as a single surrogate for infant DTP and poliomyelitis immunization, which may be oversimplified. It is possible that tetanus antibodies may not be a good surrogate for pertussis immunity because antibodies against pertussis appear to wane more rapidly over time and require an earlier booster dose.[15] However, tetanus-containing infant combination vaccines including diphtheria and pertussis antigens and inactivated poliomyelitis virus are usually administered at time of DTP immunization, poliomyelitis-specific serology is neither readily available nor standardized and the risk of acquisition of poliomyelitis is currently low in most countries.

All refugee children should have their vaccination status checked on arrival. We recommend measuring tetanus antibody titers after a single age-appropriate vaccination to assess tetanus immunity as a surrogate for previous DTP and poliomyelitis immunizations. This strategy allows the individual tailoring of vaccine schedules, avoids many unnecessary vaccinations and decreases the risk of hyperimmunization.

TABLE 2. Vaccination Strategies in Geneva, Switzerland, for Healthy Migrant Children Without Vaccination Records

Vaccine	No. of Vaccine Doses at First Visit	Follow-up Serology	Comment
Hib	Catch-up Younger than 12 mo: 3 doses 12–14 mo: 2 doses 14 mo or older: 1 dose	No	Consider all children as unimmunized
Pneumococcal vaccine	Catch-up Younger than 12 mo: 3 doses 12–23 mo: 2 doses 24 mo–59 mo: 1 dose	No	Consider all children as unimmunized
MMR	2 doses	No	Consider all children as not immune; although many children have received at least 1 dose of measles-containing vaccine, preexisting antibodies rapidly neutralize live vaccines, which cannot cause hyperimmunization
VZV	11 yr or older: if negative chickenpox history: 2 doses empirically or if negative serology	Possible at baseline to confirm lack of immunity/vaccine indication	In Switzerland, universal vaccination against VZV currently is only recommended to children 11 yr or older with no VZV history.[9]
Hepatitis B	1 booster dose, followed by serology	Yes	If anti-HBsAg-negative after booster, check HBsAg to rule out infection and complete immunization if negative
Hepatitis A	Not recommended	No	
HPV	11–15 yr: 2 doses[9] 15 yr or older: 3 doses	No	Consider all girls as not vaccinated

Hib indicates hemophilus influenzae type b; MMR, measles-mumps-rubella; VZV, varicella-zoster vaccine; HbsAg, hepatitis B surface antigen; HPV, human papillomavirus.

REFERENCES

1. Afshar M, Raju M, Ansell D, et al. Narrative review: tetanus-a health threat after natural disasters in developing countries. *Ann Intern Med*. 2011;154:329–335.
2. Viviano E, Cataldo F, Accomando S, et al. Immunization status of internationally adopted children in Italy. *Vaccine*. 2006;24:4138–4143.
3. Alagappan K, Park R, Naderi S, et al. Evaluation for tetanus antibodies in Korean-Americans living in the New York area: a pilot study. *J Immigr Minor Health*. 2009;11:105–107.
4. Tiong AC, Patel MS, Gardiner J, et al. Health issues in newly arrived African refugees attending general practice clinics in Melbourne. *Med J Aust*. 2006;185:602–606.
5. Skull SA, Ngeow JY, Hogg G, et al. Incomplete immunity and missed vaccination opportunities in East African immigrants settling in Australia. *J Immigr Minor Health*. 2008;10:263–268.
6. Germinario C, Chironna M, Quarto M, et al. Immunosurveillance on Kosovar children refugees in Southern Italy. *Vaccine*. 2000;18: 2073–2074.
7. van Schaik R, Wolfs TF, Geelen SP. Improved general health of international adoptees, but immunization status still insufficient. *Eur J Pediatr*. 2009;168:1101–1106.
8. Cohen AL, Veenstra D. Economic analysis of prevaccination serotesting compared with presumptive immunization for polio, diphtheria, and tetanus in internationally adopted and immigrant infants. *Pediatrics*. 2006;117:1650–1655.
9. Office Fédéral de la Santé Publique (OFSP). Plan de vaccination suisse 2011. Directives et recommandations. Available at:http://www.bag.admin.ch/index.html. Accessed March 12, 2012.
10. Lifson AR, Thai D, Hang K. Lack of immunization documentation in Minnesota refugees: challenges for refugee preventive health care. *J Immigr Health*. 2001;3:47–52.
11. Phillips CB, Benson J. Better primary health care for refugees - catch up immunisation. *Aust Fam Physician*. 2007;36:440–2, 444.
12. Staat MA, Stadler LP, Donauer S, et al. Serologic testing to verify the immune status of internationally adopted children against vaccine preventable diseases. *Vaccine*. 2010;28:7947–7955.
13. Posfay-Barbe KM, Kobela M, Sottas C, et al. Frequent failure of adolescent booster responses to tetanus toxoid despite infant immunization: waning of infancy-induced immune memory? *Vaccine*. 2010;28:4356–4361.
14. Paxton GA, Rice J, Davie G, et al. East African immigrant children in Australia have poor immunisation coverage. *J Paediatr Child Health*. 2011;47:888–892.
15. Heininger U, Cherry JD, Stehr K. Serologic response and antibody-titer decay in adults with pertussis. *Clin Infect Dis*. 2004;38:591–594.

ERRATUM

Fatal Wild-Type Varicella-Zoster Virus Encephalitis Without a Rash in a Vaccinated Child: ERRATUM

In the article that appeared on page 183 of volume 32, issue 3, there was an error in the key words. The key words should appear as encephalitis, varicella zoster, fatal outcome, chickenpox vaccine, zoster sine herpete.

REFERENCE

Ibraheem M, Marin M, Leung J, et al. Fatal Wild-Type Varicella-Zoster Virus Encephalitis Without a Rash in a Vaccinated Child. *Pediatr Infect Dis*. 2013;32:183–185.