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Single doses of diphtheria-tetanus-pertussis and poliomyelitis vaccines are sufficient to generate a booster-type response to tetanus in most migrant children

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ABSTRACT

Background: Immunization coverage for three doses of the diphtheria-tetanus-pertussis and poliomyelitis vaccines in infants is high worldwide, therefore despite the lack of documentation of past vaccinations, most migrant children do not require complete revaccination. Our strategy was to administer a single dose of a tetanus toxoid containing vaccine (TTCV) to migrant children followed by anti-tetanus toxoid (TT) serology to determine whether additional vaccine doses were required. Our goal was to estimate the basic TTCV coverage and to identify potential determinants of the vaccination response.

Methods: Newly arrived migrant children were prospectively enrolled between October 2014 and August 2017. We included patients aged 1–18 years with no proof of past vaccinations who accepted a single dose of TTCV. Anti-TT serology was performed after 4–6 weeks, and an anti-TT level $\geq$ 1 IU/mL was considered a booster-type antibody response with no need for additional doses of TTCV. Potential determinants of the vaccination response were identified using univariate and multivariate linear regression analyses.

Results: Two hundred and eight children were eligible for analysis. The mean age of the children was 9 (±4.5) years and 100 (48%) were female. The majority (n = 129, 62%) of the children came from the WHO Eastern Mediterranean region. Only three patients (1.4%) required additional vaccine doses. A Syrian origin ($p < 0.001$) and direct arrival primarily by airplane into Switzerland without transiting through other European countries ($p = 0.029$) associated with higher anti-TT levels in a multivariate regression model (multiple $r2 = 0.210$, $p < 0.001$).

Conclusion: A single dose of TTCV is enough to generate long-term protection in most migrant children. In the context of high basic vaccination coverage, the strategy, which consists of administration of a single dose of TTCV followed by anti-TT serology, can be considered where serotesting is available and economical.

1. Introduction

The global immunization rate for three doses of the diphtheria-tetanus-pertussis (DTP) and the poliomyelitis (Pol) vaccine at 1 year was estimated at 85% in 2017 compared to 72% and 73% in 2000 and 21 and 22% in 1980 for DTP and Pol, respectively [1]. Thus, the number of reported cases of these four diseases has decreased markedly during recent decades [1]. During infancy, DTP and Pol are usually administered in combination with other vaccines. In 1996, WHO recommended the use of a DTP-Haemophilus influenzae b (Hib)-Hepatitis B combination vaccine for children, and it is currently the most widely used childhood vaccine in the world [2,3].

The majority of migrant children followed at Lausanne University Hospital are asylum seekers who have no written proof of past immunizations, which is a situation frequently encountered in the European pediatric immigrant population. Pavlopoulou et al. [4]

Abbreviations: DTP, diphtheria-tetanus-pertussis; Pol, poliomyelitis; TT, anti-tetanus toxoid; TTCV, tetanus toxoid containing vaccines; anti-TT, antibodies against tetanus toxoid.

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reported an unknown immunization status of 79.3% (N = 238/300) in a cohort of newly arrived immigrant and refugee children in Greece between 2010 and 2013. A consensus on how to manage these situations is currently lacking in Europe. Ravensbergen et al. carried out a comparative study of the strategies followed in 32 European countries [5]. In eighteen of the countries, a person with an unknown immunization status was considered unvaccinated, but we think this is inaccurate most of the time because of the high rate of vaccinations globally. Nevertheless, the strategy of complete revaccination is applied widely in this situation [6–8], which leads to a lot of unnecessary vaccinations, in our opinion.

Because pre-vaccine serology has a high risk of underestimating actual vaccine coverage (due to decreasing antibody levels over time without the loss of memory cells) [9–11], we believe that the best strategy is to perform anti-tetanus toxoid (TT) serology after administration of a single vaccine dose and before administration of additional vaccine doses [10,12,13]. A booster-type response against TT can be considered as a surrogate marker of past DTP and Pol vaccinations because TT has been combined with other antigens for many years in the majority of national immunization plans [3,14]. Our hypothesis is that this strategy is the best way to estimate vaccine coverage and to determine a more accurate number of the necessary vaccine doses for migrant children. The primary objective of our study was to estimate the basic coverage of tetanus toxoid containing vaccines (TTCV) in a population of migrant children with undocumented immunization status. The secondary objective was to identify potential vaccination response determinants.

2. Methods

2.1. Design, setting, and population

This prospective single-center cohort study was performed in a tertiary care hospital (Lausanne University Hospital, Lausanne, Switzerland). Newly arrived migrant children and adolescents aged 1–18 years were approached for participation in this study between October 2014 and August 2017. Requirements for participation were no proof of past vaccinations (vaccination card or copy) and acceptance of TTCV at the time of the initial consultation. Legal guardians and the children (when appropriate) provided written informed consent. Patients with known immunodeficiencies and those who refused to participate were excluded. Vaccination strategies for included and not included patients were the same. Children with proof of past immunizations received catch-up immunizations according to the Swiss vaccination plan [15]. Past medical and migratory history were recorded on a common case-report form using information obtained from medical charts and interviews. Physicians and interpreters were present during completion of the questionnaires to address possible questions and misunderstandings. This study was approved by the institutional ethics committee (CER: 257/14) and conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice, and Swiss regulatory requirements.

2.2. Intervention

2.2.1. First dose of TTCV

A single dose of TTCV, which was formulated according to the age of the child, was administered:

- 1 – < 8 years: Infanrix hexa (DTPa-IPV- Hib-HB; GlaxoSmithKline, Philadelphia, PA)
- ≥ 8 years: Boostrix Polio (dTpa-IPV; GlaxoSmithKline, Philadelphia, PA) + Engerix (GlaxoSmithKline, Philadelphia, PA) B10 (8 to <11 years) or B20 (≥11 years)

2.2.2. Anti-TT serology and grouping of patients

After 4–6 weeks, serology for antibodies against tetanus toxoid (anti-TT) was performed. Blood samples were tested for anti-TT using the SERION ELISA classic Tetanus IgG kit (Institut Virion\Serion GmbH, Wurzburg, Germany) [16]. We interpreted anti-TT levels ≥ 1 IU/mL after one dose of TTCV as a booster-type response [3,17–19] because anti-TT antibodies are not detectable above this threshold after the first dose of a primary immunization [3]. An anti-TT level < 1 IU/mL was considered a primary response [3,17,18,20]. We separated our patients into two groups according to the anti-TT serology results; children with an anti-TT level ≥ 1 IU/mL and children with an anti-TT level < 1 IU/mL.

2.2.3. Additional doses of TTCV

According to Swiss immunization guidelines for migrant children [13], patients with an anti-TT level ≥ 1 IU/mL did not receive additional doses and were considered up to date for TTCV. Children with an anti-TT level between 0.5 and 1 IU/mL received one additional dose (formulated according to age) at least 6 months after the first dose, and children with an anti-TT level < 0.5 IU/mL received two additional doses [13] at least 2 months and 6 months after the first dose.

2.2.4. Other vaccinations

Two doses of MMR vaccines were administered to all migrant children without use of serologies. Vaccine response against hepatitis B was also assessed and additional doses administered when necessary [10,21]. The administration of other vaccines was carried out in accordance with the Swiss vaccination plan [15].

2.3. Statistical analysis

The Student *t*-test was used to compare continuous outcomes, and the Pearson's $\chi 2$ test was used to compare categorical and dichotomous outcomes. Univariate and multivariate linear regression analyses were performed to assess associations between anti-TT levels and demographic (e.g. gender, WHO birth region and country, age), migratory (e.g. duration of transit, exposure to conflict), and clinical (e.g. comorbidities, vaccination) variables. Preliminary analyses were conducted to ensure the normal distribution and homoscedasticity of the linear regression models. The level of significance was set at $p < 0.05$. Analyses were performed using R software v. 3.3.2 and the R Studio interface (R Studio Team, 2016).

3. Results

3.1. Population characteristics (Table 1)

Four hundred and twenty-nine newly arrived migrant children were seen in our hospital between October 2014 and August 2017. One hundred and twenty-six of them did not meet the inclusion criteria (Fig. 1). A total of 303 migrant children were eligible for inclusion, however 83 of the children were not assessed for eligibility due to the caregivers' forgetfulness or work overload. Six other patients refused to participate. Two hundred and fourteen patients agreed to participate, but six were lost to follow-up before serology could be performed (Fig. 1). The mean age of the remaining 208 patients was 9 (±4.5) years and 100 (48%) were female. The majority (n = 129, 62%) were born in the WHO Eastern Mediterranean region and came from Iraq (n = 35, 16.8%), Syria (n = 33, 15.9%), or Eritrea (n = 33, 15.9%; Fig. 2). Sixty-four percent of patients (133/208) had possessed an immunization record in the past, according to the memory of the parents. There were no differences in terms of age, gender, and WHO region of origin between

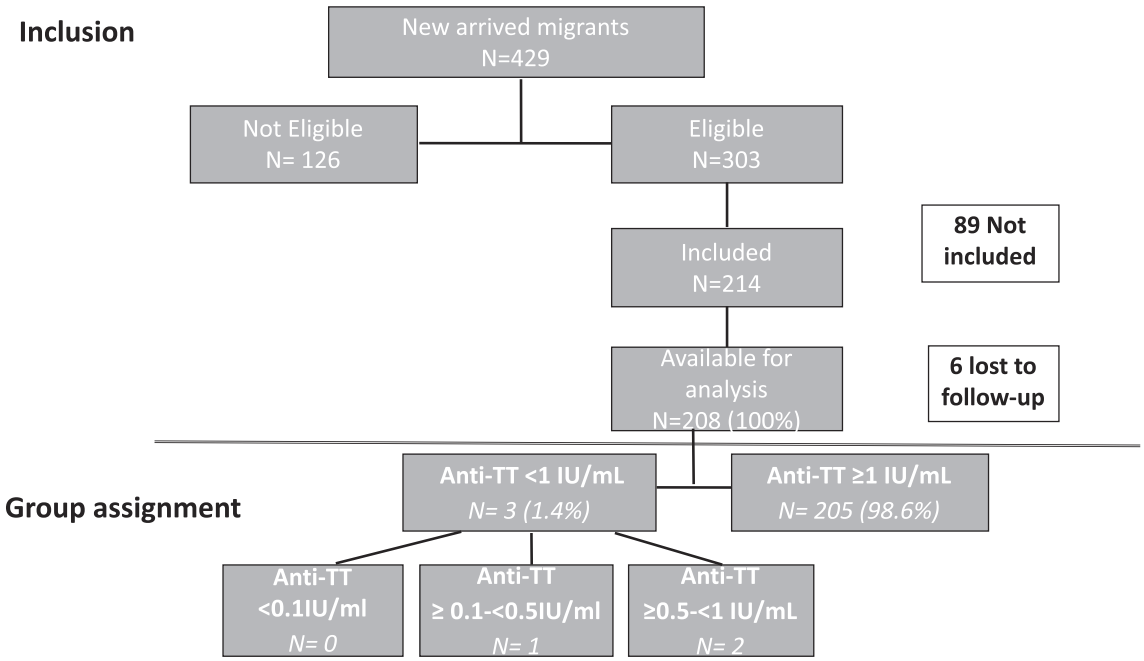

Fig. 1. Flow-chart of inclusion and group assignment. TTCV = tetanus toxoid containing vaccines, Anti-TT = antibodies against tetanus toxoid.

Table 1
Population characteristics and vaccination response.

Characteristics	n = 208 total
General	
Female, n (%)	100 (48%)
Age, mean years (±SD)	9.0 (±4.6)
Urban residence, n (%)[#]	160 (80.0%)
School attendance, n (%)[#]	129 (64%)
Conflict in country of origin, n (%)	182 (87.5%)
Unaccompanied minors, n (%):	15 (7.2%)
Birth in WHO Eastern Mediterranean region, n (%):	129 (62.0%)
Comorbidities, n (%):	16 (7.7%)
Transit	
≥ 1 European country of transit, n (%)	137 (65.9%)
Transit via refugee camp, n (%)	48 (23.1%)
Transit time, mean months (±SD)	6.5 (11.1)
Vaccination history[*,£]	
Past existence of a vaccination record[$], n (%)	133 (63.9%)
Vaccines received between 0 and 11 months, n (%)	137 (65.9%)
Vaccines received at ≥ 12 months, n (%)	101 (48.6%)
Vaccination response	
Booster-type response (anti-TT ≥ 1 IU/mL), n (%)	205 (98.6%)
GMT IU/mL (±SD)	2.48 (±0.69)

[#] Missing data: urban residence, 9; school attendance, 2.
[$] Refers to children whose immunization record was no longer available.
[£] According to the memory of the parents.
[*] Unknown information was coded as "no"; SD: standard deviation; WHO: World Health Organization; Anti-TT = antibodies against tetanus toxoid; GMT = geometrical mean titer.

included and excluded patients (data not shown). Two hundred and five children (98.6%) had an anti-TT level ≥ 1 IU/mL , and three patients (1.4%) had an anti-TT level < 1 IU/mL.

3.2. Description of patients with anti-TT level < 1 IU/mL

Two boys aged 7 years and 1 month and 9 years and 10 months came from Iraq and were in perfect health; their anti-TT levels were 0.64 and 0.33 IU/mL, respectively. Their parents reported that they had received vaccines during infancy, and both had siblings whose anti-TT levels were ≥ 1 IU/mL. The third patient came from Russia, was 4 years and 8 months old and suffered from Joubert syndrome. His anti-TT level was 0.53 IU/mL, and vaccination was initiated during his infancy but was interrupted due to his neurological disease. These three patients received additional vaccine doses according to their anti-TT levels.

3.3. Determinants of the vaccination response

Univariable linear regression analysis showed that higher anti-TT levels were associated with children from Syria (slope, 0.51; 95% CI, 0.26–0.76; $p < 0.001$) and Eritrea (slope, 0.38; 95% CI, 0.13–0.64; $p = 0.004$) than with children from other countries. There was also a correlation between migration characteristics and vaccination response. A one-month longer transit time (slope, 0.019; 95% CI, 0.00–0.02; $p = 0.046$) and direct arrival primarily by airplane into Switzerland without transiting through other European countries (slope, 0.26; 95% CI, 0.12–0.51; $p = 0.001$) were associated with higher anti-TT levels. Multivariate linear regression confirmed an association between higher anti-TT levels and birth in Syria (slope, 0.59; 95% CI, 0.26–0.76; $p < 0.001$) and direct arrival into Switzerland from the country of origin (slope, 0.26; 95% CI, 0.03–0.50; $p = 0.028$). The multivariate model explained 21% ($p < 0.001$) of the variance in the anti-TT levels. There was no statistically significant association between vaccination response and WHO region of birth, conflict in country of origin, presence of comorbidities, or past immunization history (in uni- and multivariate analysis).

3.4. Economic impact of our catch-up vaccination strategy (Table 2)

In comparison to the alternative option of complete revaccination (total cost of 106,048 CHF), our strategy (total cost of 86,882 CHF) has resulted in cost savings of 18% (Table 2).

4. Discussion

This study highlighted a very high (>95%) booster-type vaccination response against TT among migrant children after administra-

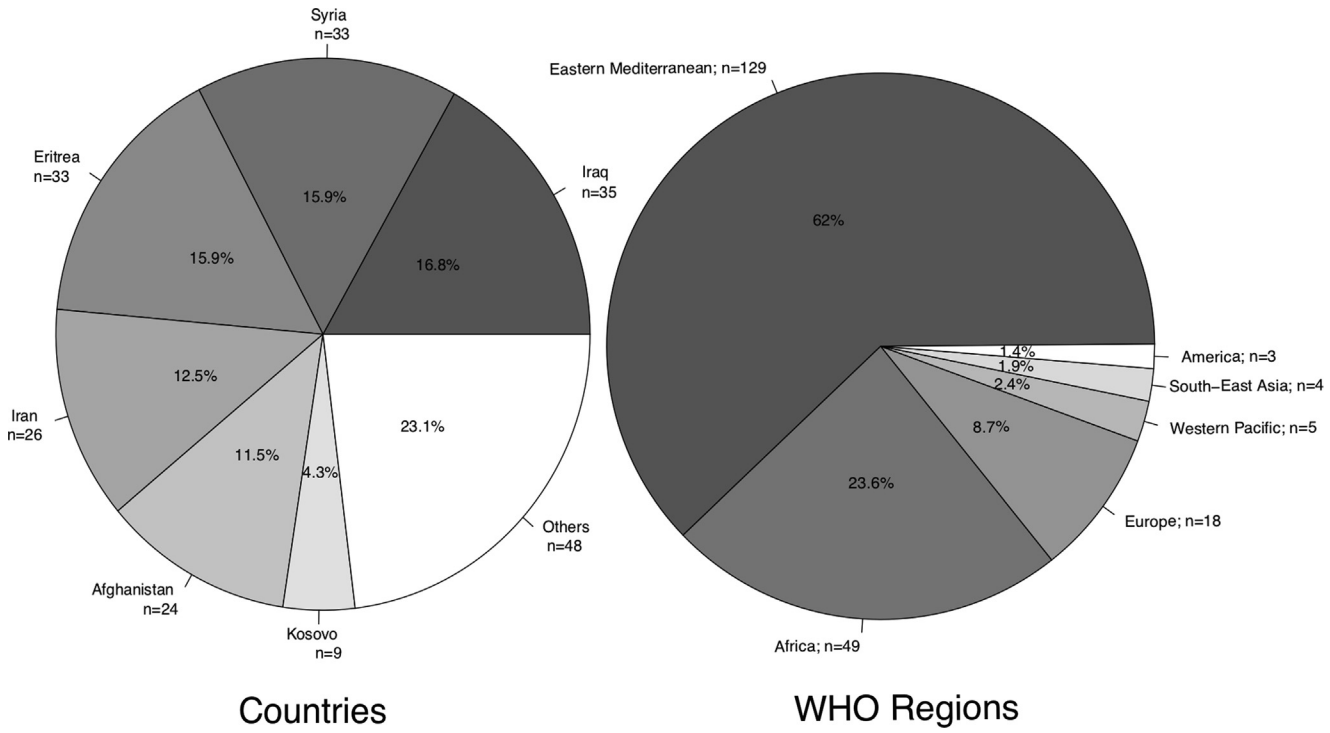

Fig. 2. Native WHO regions and countries.

tion of a single dose of TTCV. We identified two determinants of a higher antibody response, which were birth in Syria and direct arrival in Switzerland without transiting through other European countries. Our results showed a higher TTCV coverage than the world coverage estimate by the WHO; the estimated worldwide coverage for three doses of the DTP vaccine in children younger than 1 year was 85% in 2017 [1,14]. Our higher coverage results can be explained in two ways. First, patients who received only one or two doses of the vaccine in the past may have generated enough memory cells to produce a booster-type response after stimulation with the vaccine [17–19,22]. The vaccination coverage extrapolated from our results would include patients who have received three vaccine doses in the past as well as patients who have received only one or two vaccine doses in the past. Second, our population may represent a subset of children with higher vaccine coverage than the global world population [23]; the estimated 2017 coverage levels were 72%, 81%, and 94% for African, Eastern Mediterranean, and European regions, respectively [24–26]. We also know that vaccine coverage was higher in Syria before the beginning of conflict in 2011 (80% in 2010 compared to 41% in 2013 and 2015) [27], and most of our patients were born before the conflict began. This hypothesis is supported by the fact that our Syrian patients had high anti-TT levels. The higher anti-TT response observed in Syrian children may also be explained by the vaccination schedule used in Syria, which consists of three priming doses at 2, 4, and 6 months of age and a booster dose at 18 months of age, whereas Eritrea and Afghanistan use a three dose primary vaccination series for DTP at 6, 10, and 14 weeks of age without a booster dose [3,14]. In addition, migrant populations may not be representative of the global population in their countries of birth. Indeed, the migrant population may have had a higher socioeconomic status, level of education, and easier access to vaccination than the global population in their countries [26,28]. This hypothesis is supported by the fact that children with high antibody levels were more likely to arrive into Switzerland directly by air.

Table 2
Economic impact of our catch-up vaccination strategy.

Vaccination catch-up strategies	Medical visits (128 CHF)	Vaccines[#]	Serology (42 CHF)	Nursing act[$] (17 CHF)	Phone call to parents (17 CHF)	Additional costs[*]	Total cost[£] (CHF)
134 migrant children < 8 years including 2 children with anti-TT level < 1 IU/mL							
Post-booster serology	2*128*134 = 34304 CHF	79*134 = 10,586 CHF	42*134 = 5628 CHF	2*17*134 = 4556 CHF	17*134 = 2278 CHF	(79 + 17)*2 = 192 CHF	57,544 CHF
Complete revaccination	2*128*134 = 34304 CHF	3*79*134 = 31,758 CHF		17*3*134 = 6834 CHF			72,896 CHF
74 migrant children ≥ 8 years including 1 child with anti-TT level < 1 IU/mL							
Post-booster serology	2*128*74 = 18,944 CHF	47*74 = 3384 CHF	42*74 = 3108 CHF	17*2*74 = 2516 CHF	17*74 = 1258 CHF	((2*17) + (2*47))*1 = 128 CHF	29,338 CHF
Complete revaccination	2*128*74 = 18,944 CHF	3*47*74 = 10,434 CHF		17*3*74 = 3774 CHF			33,152 CHF

Swiss Francs = CHF.
[*] 1–2 vaccine doses/nursing act.
[#] Children < 8 years: Infanrix hexa® (DTPa-HepB-IPV-Hib) (79 CHF), children ≥ 8 years: Boostrix polio® (47 CHF).
[$] Immunization or blood test act.
[£] Post-booster serology: 57544 + 29338 = 86882 CHF, complete revaccination: 72896 + 33152 = 106048 CHF.

Comparison of our estimate of TTCV coverage in migrant children with existing figures in the literature is difficult because only one previous study used post-booster serology [10]. This previous study was conducted with a cohort of 55 migrant children with unknown or incomplete immunization status in Switzerland from January 2009 to May 2010. Although the children in the previous study came from different countries (mainly from Eastern Europe or Sub-Saharan Africa) than the children in our study, their results were similar to ours; in their study, 52 children (96.3%) had anti-TT levels $\geq$ 1 IU/mL after a single dose of TTCV [10]. Studies using anti-TT pre-vaccine serology to evaluate immunity to tetanus in migrant children in Europe are also scarce [9]. One study was conducted with a cohort of 52 migrant children in Germany in August 2015 [11], and they reported 28 (53.8%) migrant children with anti-TT levels $\geq$ 0.1 IU/mL and fifteen migrant children (28.8%) with anti-TT levels $\geq$ 1 IU/mL. These results show that pre-vaccine serology underestimates basic immunization coverage due to drops in anti-TT levels over time [3,17,18,20,29,30], thus pre-vaccine serology cannot be used to accurately determine vaccine coverage in migrant populations.

In the context of constantly increasing vaccine coverage, the use of post-vaccination serology seems to be the best approach to get migrant children up to date on their vaccinations. In comparison to strategies proposing full-course vaccinations, our strategy reduces the use of unnecessary vaccine doses in the majority of patients, thus most patients will only need two medical visits: for the first vaccine dose and for the serology after 4–6 weeks. For the few patients that require additional doses, one to two additional visits will be required, but this will be offset by the number of consultations and vaccine doses that will no longer be required for patients with the booster-type response. Thus, the primary benefit of our strategy is a reduction of the costs of 18%. Although it appears that vaccine protection against tetanus was high after a single booster dose, we are reluctant to omit post-booster serology because the vaccine histories were not reliable, no single determinant can reliably predict the vaccination response, and global immunization coverage may fluctuate over time.

Our study has some limitations. First, no serology other than the anti-TT serology was performed, thus our serology results were used as surrogate markers of past DTP and Pol immunizations. The risk of this methodology is an overestimation of the true coverage against diphtheria, pertussis, and poliomyelitis. However, because the tetanus vaccine is usually co-administered with other vaccines in infant immunization schedules, we believe that this risk is very low [2,3]. Furthermore, commercial serologies for pertussis and polio are difficult to interpret for the estimation of vaccine protection. Diphtheria serology, on the other hand, is fully interpretable to judge vaccine protection and it could have been added to tetanus serology. However, since we believe that virtually no migrant children have received tetanus without diphtheria, even if the magnitude of diphtheria vaccine responses is often lower [19,22,29], a significant difference in terms of the proportion of booster-type responses was not expected. Second, our results cannot be extrapolated to migrants with different countries of origin or different financial resources, as could be the case among migrant children in countries other than Switzerland. Furthermore, vaccine coverage could change over time. Finally, there were only 3 patients with primary vaccine response so that we couldn't statistically compare them with patients with booster-type responses.

5. Conclusion

Administration of a single dose of TTCV to migrant children appears to be sufficient to generate long-term protection in most migrant children. In the context of high basic vaccine coverage, our strategy, which consists of administration of a single dose of TTCV followed by anti-TT serology, can be considered for catch-up vaccinations in migrant children who lack reliable documentation of past immunizations where serotesting is conveniently available and economical. Even if our immunization coverage results cannot be extrapolated to other settings, this strategy will identify patients requiring additional doses of vaccine reliably in any situation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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