Observational Study

Medicine®

OPEN

Does vaccination ensure protection? Assessing diphtheria and tetanus antibody levels in a population of healthy children

A cross-sectional study

Ewelina Gowin, MD, PhD[a,*], Jacek Wysocki[b], Ewelina Kałużna, PhD[c,d], Bogna Świątek-Kościelna, PhD[c], Joanna Wysocka-Leszczyńska[d], Michał Michalak, PhD[e], Danuta Januszkiewicz-Lewandowska[c,d,f]

Abstract

Vaccination effectiveness is proven when the disease does not develop after a patient is exposed to the pathogen. In the case of rare diseases, vaccination effectiveness is assessed by monitoring specific antibody levels in the population. Such recurrent analyses allow the evaluation of vaccination programs. The primary schedule of diphtheria and tetanus vaccinations is similar in various countries, with differences mainly in the number and timing of booster doses. The aim of the study was to assess diphtheria and tetanus antibody concentrations in a population of healthy children.

Diphtheria and tetanus antibody levels were analyzed in a group of 324 children aged 18 to 180 months. All children were vaccinated in accordance with the Polish vaccination schedule.

Specific antibody concentrations greater than 0.1 IU/mL were considered protective against tetanus or diphtheria. Levels above 1.0 were considered to ensure long-term protection.

Protective levels of diphtheria antibodies were found in 229 patients (70.46%), and of tetanus in 306 patients (94.15%). Statistically significant differences were found in tetanus antibody levels in different age groups. Mean concentrations and the percentage of children with high tetanus antibody titers increased with age. No similar correlation was found for diphtheria antibodies. High diphtheria antibody levels co-occurred in 72% of the children with high tetanus antibody levels; 95% of the children with low tetanus antibody levels had low levels of diphtheria antibodies.

The percentage of children with protective diphtheria antibody levels is lower than that in the case of tetanus antibodies, both in Poland and abroad, but the high proportion of children without diphtheria protection in Poland is an exception. This is all the more puzzling when taking into account that Polish children are administered a total of 5 doses containing a high concentration of diphtheria toxoid, at intervals shorter than 5 years. The decrease in antibody titers occurring over time is a significant factor in vaccination program planning.

Tetanus antibody concentrations were found to be high, but responses to the diphtheria and tetanus components were divergent. The percentage of children protected against diphtheria was significantly lower than protected against tetanus.

Abbreviations: D = diphtheria, DTP = diphtheria, tetanus, pertussis, T = tetanus.

Keywords: diphtheria, tetanus, vaccination

1. Introduction

Vaccinations have been proven to be among the most effective primary prevention interventions. The operation of widespread vaccination programs is a priority in public health. Essential vaccinations include those against diphtheria and tetanus.[1]

The primary schedule of diphtheria and tetanus vaccinations is similar in various countries, with differences mainly in the number and timing of booster doses.[2–4] The diphtheria and tetanus vaccination schedule in Poland comprises a total of 7 doses: a primary course of 3 doses in the first year of life and 1 in the second year, with boosters at the ages of 6, 14, and 19. Postexposure tetanus prophylaxis is provided to adult patients, with 1 dose of tetanus toxoid administered every 10 years. In the United Kingdom, the schedule comprises a total of 5 doses—a primary course of 3 doses, as in the Polish schedule, 1 booster before beginning school and another at the end of secondary school. Likewise, in Australia, the 2-year-olds' dose is not administered. The boosters are necessary, as antibody levels decrease as time from the last dose increases.[5] The decrease in vaccine-induced antibody levels with age is a significant issue, as women tend to give birth later in their lives. A newborn's tetanus

Editor: Sarman Singh.

There are no sources of support for this study.

All the authors declare no conflicts of interests.

[a] Family Medicine Department, [b] Department of Health Promotion, Poznan University of Medical Sciences, [c] Institute of Human Genetics Polish Academy of Sciences, Department of Molecular Pathology, [d] Department of Medical Diagnostic Dobra, [e] Department of Biostatistics, Poznan University of Medical Sciences, [f] Department of Pediatric Oncology, Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland.

[*] Correspondence: Ewelina Gowin, Family Medcine Department, Poznan University of medical Sciences, 60-355 Poznan, 49 Przybyszewskiego Street, Poznan, Poland (e-mail: ewego@poczta.onet.pl).

Medicine (2016) 95:49(e5571)

Received: 28 September 2016 / Received in final form: 14 November 2016 / Accepted: 15 November 2016

http://dx.doi.org/10.1097/MD.0000000000005571

antibody level is essentially the same as the mother's. However, subsequent booster doses of tetanus and diphtheria vaccines involve a risk of local adverse effects, especially in the case of vaccines with a larger concentration of diphtheria toxoid.[4] Moreover, significant costs are incurred. The introduction of general vaccination has restricted the occurrence of certain diseases, for example, diphtheria, through a development of population immunity.[6]

The decrease in diphtheria incidence can surely be associated with the effectiveness of population immunization programs. Globally, reported cases of diphtheria have declined from 11,625 cases in 2000 to 4880 in 2011.[7,8] Currently, vaccination coverage in the Polish children population is approximately 90%, which should ensure effective protection, according to the World Health Organization.[7] Actual vaccine effectiveness is unknown. For a single patient, vaccination effectiveness is proven when the disease does not develop following exposure to the pathogen. In the mid-1990s, a diphtheria epidemic broke out in the former Soviet republics, and it was contained due to a vaccination campaign.

In 2010, 154 cases of diphtheria were reported in the following countries: the Islamic Republic of Iran, Iraq, Pakistan, Sudan, United Arab Emirates, and Yemen. In 2008, it was estimated that diphtheria was responsible of 475 deaths in countries of this region.[6,9] The last case of diphtheria in Poland was reported in 2000.[10] In an immunized population, individuals with an inadequate response to vaccines are also protected. However, migration and travel may result in new diphtheria cases in Poland, as susceptible individuals may contract the disease.

Vaccination effectiveness is proven when the disease does not develop after a patient is exposed to the pathogen. In the case of rare diseases, vaccination effectiveness is assessed by monitoring specific antibody levels in the population. Such recurrent analyses allow the evaluation of vaccination programs. An assessment of vaccine-induced antibody levels is also a part of immune system function evaluation in patients with primary and secondary immunodeficiencies, for example, those undergoing immune suppression related to cancer treatment. In a healthy population, antibody levels are assessed for comparison purposes.

The aim of the study was to assess diphtheria and tetanus antibody concentrations in a population of healthy children from the Greater Poland region.

2. Methods

Diphtheria and tetanus antibody levels were analyzed in a group of children aged 18 to 180 months. All children had been administered the 4 primary vaccine doses in accordance with the vaccination schedule in place. Samples were secured when children were hospitalized in a pediatrics ward for other tests; therefore, no separate sample collection was necessary. Exclusion criteria were chronic disease, immune suppression, or the administration of immunoglobulin preparations in the preceding 12 months. The study was approved by the Poznan University of Medical Sciences Bioethics Committee. Informed consent was signed by patients' caregivers. Anti-tetanus and anti-diphtheria immunoglobulin titers were assessed using enzyme-linked immunosorbent assays (ELISAs) in accordance with the manufacturer's guidelines (NovaLisa *Clostridium tetani* toxin IgG-ELISA and NovaLisa *Corynebacterium diphtheriae* toxin IgG-ELISA; NovaTec Immunodiagnostica GmbH, Dietzenbach, Germany). Specific antibody concentrations greater than 0.1 IU/mL were considered protective against tetanus or diphtheria (the threshold was based on the manufacturer's instructions and literature). Levels above 1.0 were considered to ensure long-term protection. Results The study group included 324 children (167 male, 157 female) aged 18 to 180 months. Mean age was 70 months, and median was 52.5 months. Protective levels (>0.1) of diphtheria antibodies were found in 229 patients (70.46%), and of tetanus antibodies in 306 patients (94.15%). Statistically significant differences were found in tetanus antibody levels in different age groups. Mean concentrations and the percentage of children with high tetanus antibody titers increased with age (Fig. 1). No similar correlation was found for diphtheria antibodies (Fig. 2). No differences were found in antibody levels between boys and girls. The distribution of antibody concentrations in the various age groups is summarized in Table 1. A correlation was shown between diphtheria antibody levels and tetanus antibody levels. High diphtheria antibody levels co-occurred in 72% of the children with high tetanus antibody levels. Forty-four percent of the children with high tetanus antibody levels had high levels of diphtheria antibodies. At the same time, 95% of the children with low tetanus antibody levels had low levels of diphtheria antibodies, and no child with low tetanus antibody levels had high diphtheria antibody levels.

For 182 children, the exact vaccine used could be determined. Thirty-seven percent of the children had been administered the primary course of vaccinations using the Polish vaccine. The group of children with low diphtheria antibody levels included both those administered combination vaccines (54%) and those vaccinated with the Polish vaccine (46%). Similarly, in the group of children with moderate antibody levels, the percentages were 56% and 44%, respectively. As to children with high diphtheria antibody titers, 90% had been administered a combination vaccine.

3. Discussion

In the study group, differences were observed in reactions to each vaccine antigen. The tetanus component is highly immunogenic and produces a good immune response.[3] Thus, in the studied population, a significant percentage of children had a protective level of tetanus antibodies. The percentage of children with a high level of tetanus antibodies (>1.0) increased with age and the number of doses administered, and was between 22% and 45%. The percentage of children with a low antibody titer was the

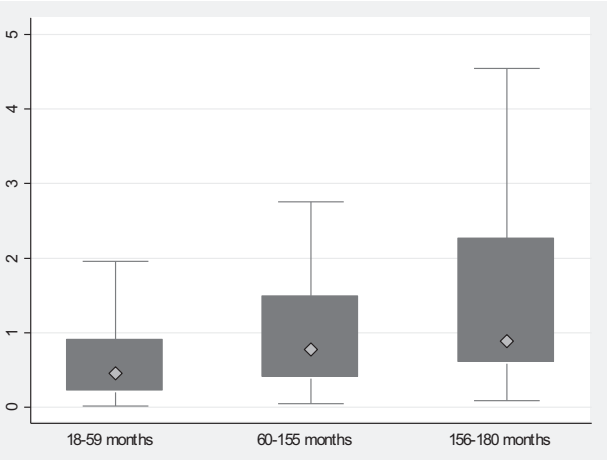

Figure 1. Mean tetanus antibody level in different age groups.

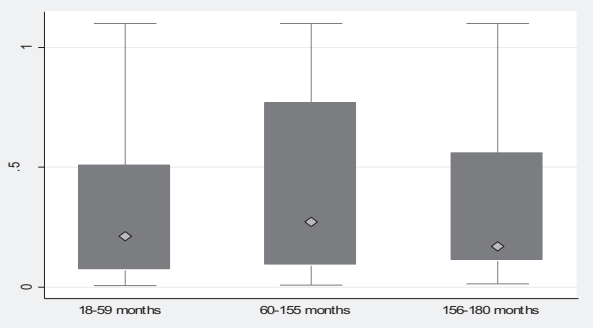

Figure 2. Mean anti-diphtheria antibodies level in different age groups.

highest in the youngest subgroup, but nonetheless did not exceed 10%. Therefore, the tetanus protection observed can be considered satisfactory.

The situation was slightly different with regard to diphtheria antibodies. Nearly 30% of the children lacked a protective level of diphtheria antibodies, despite the subsequent vaccine doses and the good response to the tetanus component. Similar results were obtained in other Polish studies, showing that up to 30% lacked the adequate protective level of diphtheria antibodies, even though a high percentage of children had undergone vaccinations in accordance with the official schedule.[11,12]

Polish children are administered various vaccines. The primary doses may be administered, free of charge, using a unique Polish Diphtheria–Tetanus–Pertussis (DTP) vaccine. Parents may also purchase combination vaccines commonly used in other countries. Here, the relationship between the use of particular vaccines and immune response was not studied, as the purpose of the study was to assess antibody concentrations in the population, and not to compare the immunogenicity of different vaccines. Such analysis would require the format of a clinical trial. Seeing as the subgroup of children with low diphtheria antibody levels included both children administered the Polish DTP vaccine and those administered other combination vaccines, the individual response to the vaccine seems very significant. An explanation of these findings would require a prospective study monitoring diphtheria antibody levels throughout the childhood in relation to the vaccine used.

The present observations on tetanus antibody levels are comparable to those reported in other countries, but what distinguishes the present population is the high percentage of children susceptible to diphtheria.[13–15]

A large European study reported percentages of children having protective diphtheria antibody levels at 75% to 99%, which are similar to those found in more recent studies.[6] As many as 86% 5-year-old Italian children had a protective diphtheria antibody titer before subsequent vaccination.[13] The response was similar following vaccination with a large and reduced concentration of the diphtheria (D or d) component. No difference between the D and d dosages was found in France, either.[14] In the study by Tomovici et al,[15] 94.5% of teenagers tested before a booster injection had a protective diphtheria antibody titer, and 100% had a protective antibody titer against tetanus. After the booster injection, all patients developed a protective antibody titer, which persisted for the following 10 years. In a Canadian study by Embree et al,[5] protective concentrations of antibodies against diphtheria and tetanus were found in 82% and 99% of 11-year-olds (5 years following their last tetanus–diphtheria vaccination), respectively. One month following a booster injection, these percentages reached 100% and remained at that level for 10 years. In a Dutch study, the percentage of children above 1 year of age who lacked a protective level of diphtheria antibodies did not exceed 3%.[16] In the study by Paulke-Korinek et al[17] on a group of 338 children, 81.4% were protected against diphtheria and 96.4% against tetanus. The antibody concentration was dependent on time from the vaccination. Comparisons of antibody titers between children from various countries are made difficult by differences in vaccination schedules. The choice of age groups and the time from last dose have a significant impact on results. Comparisons between adult populations are easier, as no more booster doses are provided for in vaccination schedules.

The percentage of children with protective diphtheria antibody levels is lower than that in the case of tetanus antibodies, both in Poland and abroad, but the high proportion of children without diphtheria protection in Poland is an exception. This is all the more puzzling when taking into account that Polish children are administered a total of 5 doses containing a high concentration of diphtheria toxoid, at intervals shorter than 5 years. Numerous papers evaluating the effectiveness of particular vaccines are available, but the data are mostly found in clinical trials performed for vaccine manufacturers and cannot be directly projected onto a population.

The decrease in antibody titers occurring over time is a significant factor in vaccination program planning. It is estimated that immune responses against diphtheria and tetanus persist for a minimum of 5 years following vaccination.[18,19] In Poland, the interval between doses 4 and 5 and between doses 6 and 7 is shorter than 5 years. The 7-dose schedule for diphtheria and tetanus vaccinations has not been updated for years. In the past, the obligatory vaccinations were performed in schools. Dose no. 6 is administered at the age of 14 (which in the former educational system corresponded to the final year of primary education), and the last one is administered at the age of 18 or 19. Currently, vaccines are administered in family doctor practices,

Table 1

Distribution of diphtheria and tetanus antibodies in different age groups.

	N = 324 (%n)	18–59 mo (n = 172)	60–155 mo (n = 115)	156–180 mo (n = 37)
D < 0.1	95 (29.32%)	57 (33.14%)	30 (26.96%)	8 (21.62%)
D 0.1–1.0	172 (53.09%)	87 (50.58%)	60 (51.30%)	25 (67.57%)
D > 1.0	57 (17.59%)	28 (16.28%)	25 (21.74%)	4 (10.81%)
T 0.01–0.1	19 (5.86%)	16 (9.30%)	2 (1.74%)	1 (2.70%)
T 0.11–1.0	211 (65.12%)	118 (68.60%)	74 (64.35%)	19 (51.35%)
T > 1.0	94 (29.01%)	38 (22.09%)	39 (33.91%)	17 (45.95%)

and not in schools; moreover, the educational system is organized differently.

In conclusion, it should be emphasized that tetanus antibody concentrations were found to be high in the studied population, but responses to the diphtheria and tetanus components of the vaccine (administered simultaneously) were divergent. The percentage of children protected against diphtheria was significantly lower than the percentage of children protected against tetanus. The concentration of antibodies against tetanus increased with age and with subsequent doses, while no such correlation was seen in the case of diphtheria antibodies. The findings, compared with those reported in other countries, may give rise to questions about the need for modifications in the vaccination program—a different dose schedule, longer intervals between doses (e.g., 10 years), or a reduced number of doses, for example, forgoing the dose administered to 14-year-olds.

References

[1] Pickering LK, Baker CJ, Freed GL, et al. Immunization programs for infants, children, adolescents, and adults: clinical practice guidelines by the Infectious Diseases Society of America; Infectious Diseases Society of America. Clin Infect Dis 2009;49:817–40.

[2] Galazka AM. The immunological basis for immunization series, module 3: tetanus. Global programme for vaccines and immunization, Expanded Programme on Immunization. Geneva: World Health Organization; 1993.

[3] Advisory Committee on Immunization PracticesUpdated recommendations for use of tetanus toxoid, diphtheria toxoid and acellular pertussis vaccine from the Advisory Committee on Immunization Practices 2010. MMWR Morb Mortal Wkly Rep 2011;60:13–5.

[4] Sheifele DW, Ochnio JJ. The Immunological Basis for Immunization Series, Module 2: Diphtheria Update 2009. Geneva:World Health Organization; 2009.

[5] Embree J, Law B, Voloshen T, et al. Immunogenicity, safety, and antibody persistence at 3, 5, and 10 years post vaccination in adolescents randomized to booster immunization with a combined tetanus, diphtheria, 5- component acellular pertussis, and inactivated poliomyelitis vaccine administered with a hepatitis B virus vaccine concurrently or 1 month apart. Clin Vaccine Immunol 2015;22:282–90.

[6] Edmunds WJ, Pebody RG, Aggerback H, et al. The seroepidemiology of diphtheria in Western Europe. ESEN Project. European Sero-Epidemiology Network. Epidemiol Infect 2000;125:113–25.

[7] Gałązka A. The changing epidemiology of diphtheria in the vaccine era. J Infect Dis 2000;181(Suppl 1):S2–9.

[8] Tiwari TSP. Brunette GW. Diphtheria. CDC Health Information for International Travel 2012: Yellow Book. New York:Oxford University Press; 2012. 162–4.

[9] Wagner KS, White JM, Lucenko I, et al. And on behalf of the Diphtheria Surveillance Network: diphtheria in the postepidemic period, Europe, 2000–2009. Emerg Infect Dis 2012;18:217–25.

[10] NIPH-NIH. Reports on Cases of Infectious Diseases and Poisonings in Poland. Available at: http://www.pzh.gov.pl/oldpage/epimeld/index_a.html#01. Accessed 1st May 2016

[11] Zasada A, Rastawicki W, Rokosz N, et al. Seroprevalence of diphtheria toxoid IgG antibodies in children, adolescents and adults in Poland. BMC Infect Dis 2013;13:551.

[12] Walory J, Grzesiowski P, Hryniewicz W. The prevalence of diphtheria immunity in healthy population in Poland. Epidemiol Infect 2001;126:225–30.

[13] Ferrera G, Cuccia M, Mereu G, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated polio virus vaccine co-administered with measles-mumps-rubella-varicella vaccine. A randomized, controlled trial in children primed according to a 2+1 schedule in infancy. Hum Vacc Immunother 2012;8:355–62.

[14] Launay O, Toneatti C, Bernede C, et al. Antibodies to tetanus, diphtheria and pertussis among healthy adults vaccinated according to the French vaccination recommendations. Hum Vaccin 2009;5:341–6.

[15] Tomovici A, Barreto L, Zickler P, et al. Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. Vaccine 2012;30:2647–53.

[16] De Melker HE, Berbers GAM, Nagelkerke NJD, et al. Diphtheria antitoxin levels in the Netherlands: a population-based study. Emerg Infect Dis 1999;5:694–700.

[17] Paulke-Korinek M, Fischmeister G, Grac A, et al. Persistence of antibodies in 4–8 year old Austrian children after vaccination with hexavalent DTaP-HBV-IPV/Hib and MMR vaccines. Vaccine 2011;29:5130–6.

[18] Barreto L, Guasparini R, Meekison W, et al. Humoral immunity 5 years after booster immunization with an adolescent and adult for- mulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. Vaccine 2007;25:8172–9.

[19] Gajdos V, Soubeyrand B, Vidor E, et al. Immunogenicity and safety of combined adsorbed low-dose diphtheria, tetanus and inactivated poliovirus vaccine (REVAXIS) versus combined diphtheria, tetanus and inactivated polio virus vaccine (DT Polio) given as a booster dose at 6 years of age. Hum Vaccin 2011;7:549–56.