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Seroprevalence of IgG antibodies against tetanus toxoid among different age groups in Poland

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Abstract

Introduction and Objective. Vaccination is the most effective and reliable strategy for preventing the morbidity of tetanus. The aim of the study is to investigate the seroprevalence of antibodies to tetanus toxoid among healthy persons across all age groups to determine the level of vaccine-induced immunity in the population, and to identify which age group should be targeted for a booster dose.

Materials and method. A total of 2,842 serum samples collected between 2010 – 2019 from individuals aged from 1 month – 97 years were investigated. Anti-tetanus IgG antibody concentrations (IU/ml) were measured by an enzyme-linked immunosorbent assay. In addition, the avidity of antibodies was determined using an in-house ELISA.

Results. The results showed that among the 2,842 individuals, 147 (5.2%) had anti-tetanus toxoid IgG antibody levels below 0.1 IU/ml and another 1,519 (53.4%) subjects showed only basic protection (0.1–1.0 IU/ml) and needed immediate booster. High levels of anti-tetanus toxoid IgG antibodies (>1.0 IU/ml) were found more often in young adults at the age 21–40 years (55.5%, GMT=1.15). Importantly, these antibodies also had the highest avidity. With age, the percentage of high positives decreased, as well as the geometric mean and avidity of antibodies, reaching the lowest level in subjects over 70 years of age (13.3%; GMT=0.19). Characteristically, a higher percentage of high positive results was observed in men (42.6%) than in women (34.3%).

Conclusions. The study showed adequate immunity levels to tetanus amongst the Polish population, especially in children, adolescents, and young adults. However, those from older age groups should receive booster doses of the vaccine.

Key words

vaccination, IgG antibodies, tetanus, tetanus toxoid

INTRODUCTION

Tetanus is a highly dangerous, infectious disease of the nervous system caused by a neurotoxin (tetanospasmin) produced by the spore forming anaerobic *Clostridium tetani*. The main reservoir of *C. tetani* is dust, water, soil contaminated with animal faeces, animal digestive, fertilizers [1, 2, 3]. Symptoms of tetanus can be varied and may be generalized, mild, or local [4, 5]. The main complications of tetanus are respiratory and heart failure, and mental retardation. Neonatal tetanus is special form which often ends in death. The group at increased risk of developing tetanus includes people over 60 years of age [6], people working in the health service, in military service, animal breeders, sewage treatment plant workers, farmers and gardeners [7]. Pregnant women are a special group because booster vaccinations against tetanus are important for the active immunity of the mother, and for passive immunity of the neonate to infectious disease.

According to the WHO data, about 140,000 cases of tetanus were recorded worldwide in the period 2008- 2018. Currently, it is the biggest problem in Asia, Africa and South America [8]. In the EU, tetanus incidence is very low due to widespread vaccination programmes. The highest risk of tetanus in Europe is among the elderly, the immunocompromised and among intravenous drug users.

The best method of preventing tetanus is to use immunoprophylaxis through active immunization [9]. Due to the lack of importance of the population's collective immunity to tetanus, in unvaccinated persons or with too low levels of anti-tetanus antibodies (e.g. due to the lack of booster vaccinations or disorders of the immune system), there is a risk of disease occurrence if the wound is contaminated with tetanus [10]. After the primary vaccination, immunity declines over time, and booster doses are recommended every 10 years.

In Poland, according to the Preventive Vaccination Programme, all children should receive 4 doses of DTP vaccine at: 2, 3–4, 5–6 and 16–18 months of age (primary vaccination) with DTP vaccine (free of charge) or DTaP vaccine (paid) and a booster dose (DTaP) at 6 years of age, and a dose of dTap vaccine at 14 years of age. The last dose of diphtheria, tetanus and pertussis vaccine is given at 19 years of age as a mandatory vaccination – Td or recommended vaccination – Tdap [11].

Knowledge of the level of IgG antibodies, as well as antibody avidity and the functional strength with which an antibody binds to an antigen, are important qualitative characteristics of immunity, as it will provide information on the efficacy of the anti-tetanus immunization schedule [12]. Data on the prevalence of protective antibodies in children, adolescents

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and adults in Poland are currently limited. Therefore, the aim of this study was to determine the protective level and avidity of IgG antibodies to tetanus toxoid in subjects in different age groups of the Polish population.

MATERIALS AND METHOD

Approval of the Bioethics Committee. The studies were approved by the Bioethics Committee at the National Institute of Public Health – National Institute of Hygiene in Warsaw (Opinion Nos.: 6/2012 of 04/10/2012 and 1/2017 of 09/03/2017). The study was conducted in accordance with the World Medical Association Declaration of Helsinki for ethical principles for medical research involving human subjects.

Study population and serum samples. The specific anti-tetanus toxoid antibodies were measured in 2,842 serum samples collected between 2010 – 2019 from individuals living in 5 macroregions of Poland (north-west, Masovian, central, south-west, eastern). The serum bank comprised frozen samples (at -70°C), collected during different epidemiological or diagnostic studies conducted at the National Institute of Public Health – National Institute of Hygiene in Warsaw. The serum samples were selected randomly from the data bank. Data on gender as well as on age were available from all individuals – 1,465 females and 1,377 males), aged from 1 month to 97 years (median, 20.9 years). Among the tested serum samples, 86 were collected from pregnant women or women planning to become pregnant.

Commercial ELISA for measuring of anti-tetanus IgG. A commercial enzyme-linked immunosorbent assay (ELISA) kit (IBL International GmbH, Hamburg, Germany (Cat. No. RE 56901) was performed according to the manufacturer's recommendations. The level of antibodies in International Units values (IU/mL) were determined from the curve plotted on the basis of the 5 control sera: Calibrator A (0 IU/ml), Calibrator B (0.1 IU/ml), Calibrator C (1 IU/ml), Calibrator D (2.5 IU/ml), Calibrator E-5.0 IU/ml). The 5 Calibrators were calibrated against the WHO 1st International Standard – TE3. Briefly, 100 µl of dilution serum samples (1:101) were placed into each antigen-coated well and incubated for 60 min at room temperature. The solution was then removed and the wells washed 3 times with 300 µl of wash buffer. Next, 100 µl of enzyme conjugate was added into the wells and the plate incubated for 30 min at room temperature. After incubation, the wells were washed again 3 times. Then, 100 µl of substrate solution was added into the each well, and the plate incubated for 20 min in the dark. In the last step, after adding of 100 µl of stop solution, the optical density of the solution was checked at 450 nm. Samples which showed concentrations above the highest standard were further diluted. Results of samples with higher predilution were multiplied by the dilution factor. According to the manufacturer's recommendation, the results were divided into 4 groups: <0.1 IU/ml (indicating immediate basic immunization), 0.1–1.0 IU/ml (sufficient level, control after 1–2 years is recommended), >1.0–5.0 IU/ml (sufficient level, control after 2–4 years is recommended), and >5.0 IU/ml (sufficient level, control after 4–8 years is recommended).

In-house ELISA for measuring avidity of antibodies. For detection of avidity of IgG antibodies to tetanus toxoid, an in-house ELISA was standardized. Briefly, 2 flat-bottomed 96 well polystyrene microtitration plates (MaxiSorp, Nunc – Immuno Plate; Cat. No. 442404) were coated overnight at 4°C with 100 µL/well of toxoid WHO (Non-WHO Reference Material Tetanus Toxoid, Non-Adsorbed, No. 02/232), at a final concentration of 0.5 Lf/ml in sterile Phosphate Buffered Saline (PBS, pH 7.4). The next day, the plates were washed in PBS+Tween 20 (PBS-T 0.1%) and blocked for 1.5 h at room temperature using a 400 µL of blocking buffer (BB) containing 5% skimmed milk powder + Tween-20 in PBS. Then, 100 µL of 2-fold serially diluted human serum (dilutions 1:100 – 1:12800) in diluent buffer (0.5% skimmed milk powder + Tween-20 in PBS. The plates were then washed 4 times using washing buffer. To evaluate the avidity of the antibodies, an ammonium thiocyanate (NH_4SCN at concentration 4 M) was added in a volume of 100 µl to each well of one plate. As a control, 100 µl of PBST solution was applied to each well of the second plate. Both plates were incubated at 37 °C for 30 min. To completely remove the denaturing substance and to maintain the same number of washes, both plates were washed 4 times with PBST buffer and dried on a towel. Then, 100 µl of conjugate (Dako IgG Conjugate Polyclonal Rabbit Anti-Human IgG/HRP No. PO214) diluted in 0.5% PBSTM of (1/5,000 dilution) was added to each well of both plates and incubated for 60 min. at 37 °C. After incubation, the wells of the plates were washed 6 times with PBST buffer. Enzymatic reaction was detected with HRP substrate TMB (3,3`,5,5` – Tetramethylbenzidine, Sigma-Aldrich; Cat. No. 860336). Colour development was stopped by adding 150 µL of 1N sulphuric acid (H_2SO_4) and absorbance values were recorded at 450 nm using a microplate reader (Asys Hitech Expert Plus, Biogenet). Antibody avidity was index (AI) measured as the ratio of the optical density value obtained in the reaction with the dissociating solution (NH_4SCN) to the value obtained for the control solution (without ammonium thiocyanate). The AI avidity index was interpreted arbitrarily according to the range: < 30AI (low avidity), 30–50 AI (medium avidity), and > 50 AI (high avidity) [13].

Statistical analysis. The statistical significance of the differences in the frequency of detection of anti-tetanus antibodies in particular groups of people depending on gender and age, was analyzed by Fisher's exact probability test with Yates' correction. A P-value < 0.05 was considered significant. The arithmetic mean titers, standard deviations and geometric mean titers (GMT) were calculated using Excel.

RESULTS

The study population was divided into 9 age groups: 0–5 years, 6–13, 14–20, 21–30, 31–40, 41–50, 51–60, 61–70 and >70 years. The distribution of antibodies, arithmetic and geometric mean titers, standard deviation and mediana in subjects from different age groups are presented in Table 1. The results showed that among the 2,842 individuals, 147 (5.2%) had anti-tetanus toxoid IgG antibody levels below 0.1 IU/ml. Another 1,519 (53.4%) subjects showed low basic protection (0.1–1.0 IU/ml) and needed control after 1–2 years. The effects of the each booster dose were clearly visible,

Table 1. Distribution of sero-protection of IgG antibodies to tetanus toxoid in the Polish population, according to age group

Age groups (years)	No. of tested persons	No. (percentage) of persons with level of IgG antibodies to tetanus toxoid (IU/ml)				Geometric mean titer (IU/ml)	Arithmetic mean titer (IU/ml)	Standard deviation (IU/ml)	Mediana (IU/ml)
		< 0.1	0.1–1.0	1.0–5.0	>5.0				
0–5	370	14 (3.8%)	175 (47.3%)	156 (42.2%)	25 (6.8%)	0.91	1.74	1.69	0.93
6–13	1,347	34 (2.5%)	828 (61.5%)	447 (33.2%)	38 (2.8%)	0.64	1.16	1.27	0.64
14–20	225	7 (3.1%)	81 (36%)	126 (56.0%)*	11 (4.9%)	1.13	1.92	1.6	1.47
21–30	192	1 (0.5%)	76 (39.6%)	113 (58.9%)	2 (1.0%)	1.16	1.68	1.27	1.39
31–40	212	3 (1.4%)	95 (44.8%)	110 (51.9%)	4 (1.9%)	1.0	1.53	1.31	1.08
41–50	149	12 (8.1%)	66 (44.3%)	67 (45.0%)*	4 (2.7%)	0.69	1.35	1.32	0.87
51–60	135	17 (12.6%)	82 (60.7%)	35 (25.9%)	1 (0.7%)	0.38	0.83	1.06	0.35
61–70	137	30 (21.9%)	81 (59.1%)	26 (19.0%)	-	0.27	0.6	0.92	0.22
≥ 71	75	29 (38.7%)	35 (46.7%)	10 (13.3%)	1 (1.3%)	0.19	0.52	0.96	0.10
Total	2,842	147 (5.2%)	1,519 (53.4%)	1,090 (38.4%)	86 (3.0%)	0.69	1.31	1.38	0.73

*Statistical significant (p< 0.05)

causing the maximum protection level in individuals aged 21–30 years (GMT = 1.16 IU/ml). In the older age groups, there was a decrease of GMT values, as well as a decrease in the percentage of subjects with protective levels of anti-diphtheria toxoid IgG antibodies. The lowest level of antibodies was found in subjects over 70 years of age. Importantly, in children aged 6–13 years, the average level of antibodies was lower than in children aged 0–5 years. In adolescents aged 14–20 years, the detection of IgG antibodies to tetanus toxoid at a level exceeding ≥ 1.0 IU/ml was statistically significantly more frequent than in children aged 6–13 (chi square = 48.89, p<0.05). Also, statistically significantly more often, post-vaccination antibodies to tetanus toxoid at levels exceeding the value ≥1.0 IU/ml were detected in adults aged 41–50 years than in those aged 51–60 years (chi square = 12.4).

Analysis of the results obtained during the examination of all 2,842 serum samples showed that the geometric mean value of the post-vaccination antibody level for tetanus toxoid is 0.69 IU/ml. To sum-up, in accordance with the current recommendations regarding the protective level of post-vaccination antibodies to tetanus toxoid (≥ 0.1 IU/ml), as many as 94.8% of respondents showed a value defined as a safe protective level for tetanus, of which 41.2% persons showed a high value (> 1.0 IU / ml).

Avidity analysis was performed on the basis of serum samples obtained from 496 adults over 20 years old (Tab. 2). Similar to the level of antibodies to tetanus toxoid, the highest values of the avidity index (GM = 47) were obtained in subject aged 21–30 years. High antibody avidity (>50 A/I) was present in 58.1% of subjects in this age group. In subjects from the older age groups, the avidity index decreased parallel to the geometric mean of the antibody level. The lowest value of the avidity index (GM =14) was detected in the oldest persons, over 70 years of age. Statistical analysis showed that in adults aged 21–30 years, a high IgG avidity index for tetanus toxoid was significantly more often detected than in adults over 40 years of age (p<0.05).

Figure 2 shows the occurrence of post-vaccination IgG antibodies to tetanus toxoid depending on age, but taking into account the gender of the examined persons. Interestingly, in almost all age groups, higher values of the geometric mean

Table 2. Avidity of IgG antibodies to tetanus toxoid in adult Polish population. according to age group

Age group (years)	No. of tested persons	No. (percentage) of persons with IgG avidity index (A/I)			Geometric mean of avidity index
		Low <30%	*Medium 30–50%*	*High >50%*	
21–30	93	16 (17.2%)	23 (24.7%)	54 (58.1%)*	47
31–40	110	25 (22.7%)	26 (23.6%)	59 (53.6%)	44
41–50	92	36 (39.1%)	24 (26.1%)	32 (34.8%)	31
51–60	80	46 (57.5%)	17 (21.2%)	17 (21.2%)	24
61–70	78	52 (66.7%)	14 (17.9%)	12 (15.4%)	20
≥ 71	43	33 (76.7%)	5 (11.6%)	5 (11.6%)	14

*Statistical significant (p< 0.05)

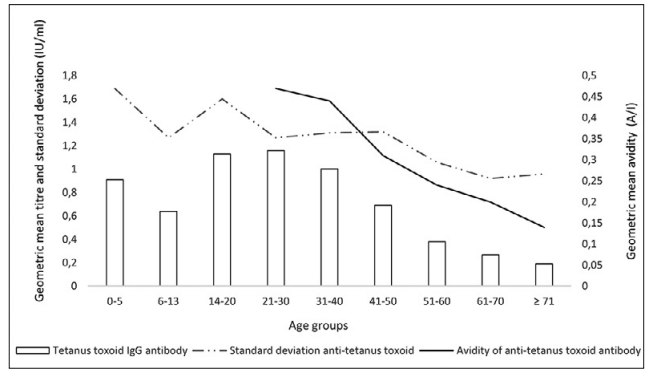

Figure 1. Geometric mean concentration of the level (IU/ml), standard deviation (IU/ml) and avidity (A/I) of IgG antibodies to tetanus toxoid in the Polish population, according to age groups

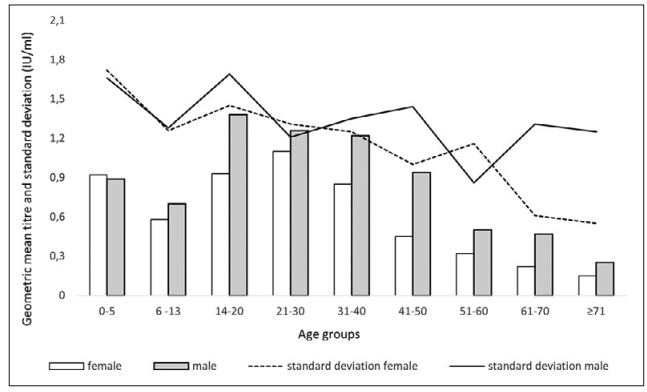

Figure 2. Prevalence of IgG antibodies to tetanus toxoid and standard deviation by gender and age

level of vaccine antibodies were found in men than in women. The greatest differences in the values of the geometric mean were observed in adolescents and young adults ($p<0.05$).

The occurrence of vaccine IgG antibodies to tetanus toxoid was also compared in pregnant women aged 21–40 years and in non-pregnant women of the same age (control group). A clearly higher average level of post-vaccination antibodies was diagnosed in pregnant women than in the control group (GMT = 1.09 and GMT = 0.67, respectively).

DISCUSSION

Vaccination is believed to be the most cost-effective strategy for the prevention of tetanus [9]. The DTP (the diphtheria-tetanus-pertussis vaccine) vaccination coverage in children in Poland was estimated to be 99% since 2002, and subsequent years estimated at ≥ 95%. In Poland, tetanus vaccinations are included in the Compulsory Vaccination Programme and include 4 doses of the primary vaccination at the age of 2, 3–4, 5–6, 16–18 months, and 3 booster vaccinations at the age of 6, 14 and 19 years [11, 14, 15, 16]. Many authors point out that the protective level of tetanus vaccine antibodies lasts for an average of 10 years, and in order to maintain this level, it is recommended to administer booster doses in adults every 10 years [6, 11, 15]. Unfortunately, in practice, booster vaccinations in adults in Poland are very rare. For this reason, there is a risk that the antibody post-vaccination level in older people may be insufficient to protect against tetanus.

The presented study showed significant differences in the level of antibodies to tetanus toxoid depending on the age of subjects. Generally, the antibody level in the Polish population increased with each booster dose and achieved the highest level (GMT =1.16 IU/ml) in young adults after the last booster administered at age 21–30 years. Then, a gradual decrease in antibody levels can be observed with the age of the test subjects. The lowest level of anti-tetanus antibodies was found in subjects aged 61–70 years (GMT = 0.27 IU/ml) and over 70 years (GMT = 0.19 IU/ml). It should be borne in mind that such a low level of protective antibodies in these age groups increases the risk of developing tetanus. Many authors point to the fact that the high percentage of vaccinating children and adolescents means that tetanus is most often diagnosed in the elderly [17, 18, 19, 20, 21]. The best evidence for this is the research conducted in 1988–2000 in New Zealand, where as much as 48.3% of all tetanus cases concerned people over 65 years of age [22].

In the current study, higher levels of anti-tetanus antibodies were found in men than in women. This may be the reason for the higher incidence of tetanus among women, especially in older age, worldwide. Studies conducted by Valentio et al. [23] in 1996–1999 in Italy showed that 90.6% of patients with tetanus were women and only 9.4% men. Studies conducted in Australia in 1993–2003 by Quinn et al. [20], also showed that women (81 cases) suffered from tetanus more often than men (57 cases). Similar results were also obtained by Pedalino et al. [24], who analyzed the incidence of tetanus in Italy in 1971–2000, and showed that the most common cases of tetanus were people over 64 years of age, and that women (1744 cases) were more often affected than men (789 cases).

Differences in the frequency of detection of the protective level of tetanus antibodies depending on gender may be related to the compulsory vaccination of men during military service, as well as the frequent performance of occupations in which men are exposed to injuries and the associated risk of *C. tetani* infection. These professions include, among others, animal breeders, employees of sewage treatment plants, farmers and gardeners [25, 26, 27, 28, 29, 30].

The vaccination of women of childbearing age with TT is assumed to be the most cost-effective strategy for the prevention neonatal tetanus. Prevention of tetanus during pregnancy depends on the vaccination history. According to recommendations of the American College of Obstetricians and Gynecologists, pregnant women without a documented vaccination history should receive at least one dose of the vaccine and one dose as soon as possible in the third trimester of pregnancy [31]. Maternal immunization protects the mother and foetus from disease, and protects the young infant through transplacental transfer of maternal antibody for the first months of life [32]. The efficiency of transplacental transfer is dependent on a range of factors including the total IgG concentration in maternal blood, the type of vaccine, timing of vaccine administration during gestation, and gestational age of the foetus at birth [33].

In the presented study it was found that the geometric mean value of the antibody level was significantly higher (GMT =1.09 IU/ml) in pregnant women than in women from the control group and in the same age group (GMT =0.67 IU/ml). A significantly higher mean antibody level in pregnant than non-pregnant women found in this study was due to the fact that most women in Poland are vaccinated with a booster dose of the anti-tetanus vaccine during pregnancy. Thus, the current finding provides evidence that pregnant women do receive an adequate immune response to tetanus. The findings of the current study are similar to those reported by other researchers.

A sero-survey by Halperin et al. [34] and Ladhani et al. [35] confirmed the validity of vaccinating women in the third trimester pregnancy, because transfer across the placenta is greatest during this period maternal antibodies, observing higher values in newborn babies than in their mothers. Similar findings were reported from Meng et al. [36] who also confirmed the validity of vaccinating pregnant women, obtaining results of the level of anti-tetanus antibodies in women who did not receive a booster dose of the vaccine (77.1% of women did not have a protective level of antibodies) and their children (73% did not have a protective level of antibodies).

Another aim of the current study was to determine the avidity index of IgG antibodies. A very important observation was the fact that in adults over 40 years of age, a consistent, significant decrease in the avidity of IgG antibodies was seen. The decrease in the level of vaccine antibodies and the decrease in the avidity of these antibodies in persons from older age groups make these persons particularly vulnerable to contracting tetanus. All of this strongly suggests that these individuals need booster doses of the tetanus vaccine.

CONCLUSIONS

The study demonstrated that almost 95% of subjects in Poland had anti-tetanus antibodies. The maximum level of post-vaccination anti-tetanus antibodies was observed at the end of the vaccination course, in persons aged 21–30, and with higher levels in almost all age groups, and found more

frequently in men than in women. However, the low levels of antibodies and their avidity in subject over 60 years of age strongly suggest the need for booster doses of tetanus vaccines in older persons.

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