Tetanus and Diphtheria Immunity in Refugees in Europe in 2015

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Key words

Vaccination, Refugee, Tetanus, Diphtheria, Immunity, Asylum, Vaccine-preventable diseases

Abbreviations

EU: European Union, IgG: immunoglobulin G, TD: tetanus, diphtheria, VPD: vaccine-preventable diseases, WHO: World Health Organization, UNHCR: United Nations High Commissioner for Refugees, UNICEF: United Nations Children´s Fund

Authorship contributions

Alexandra Jablonka and Georg Behrens contributed equally to this work.

Participated in research design: Alexandra Jablonka, Georg MN Behrens, Reinhold RE Schmidt

Conducted collection and analyses of samples: Routine clinical care

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Wrote or contributed to writing of the manuscript: All authors

Conflict of interest statement

None to specify

Abstract

Background:

Current political crises in the Middle East and economic discrepancies led millions of people to leave their home countries and to flee to Western Europe. This development raises unexpected challenges for receiving health care systems. Although pan-European initiatives strive for updated and optimized vaccination strategies, little data on immunity against vaccine-preventable diseases in the current refugee population exist.

Methods:

We quantified serum IgG against tetanus and diphtheria (TD) in n=678 refugees currently seeking shelter in six German refugee centers.

Findings:

Reflecting current migration statistics in Europe, the median age within the cohort was 26 years, with only 23.9% of female subjects. Insufficient IgG levels without long term protection against tetanus were found in 56.3% of all refugees. 76.1% of refugees had no long term protection against diphtheria. 47.7% of subjects needed immediate vaccination against tetanus, and 47.7% against diphtheria. For both diseases, an age dependent decline in protective immunity occurred.

Interpretation:

We observed a considerably low rate of tetanus protected refugees, and the frequency of diphtheria immune refugees was far from sufficient to provide herd immunity. These findings strongly support recent intentions to implement and enforce stringent guidelines for refugee vaccination in the current crisis.

Introduction

Current political and economic crises in the Middle East, Eastern Europe and Northern Africa led millions of people to leave their home countries and migrate to Western Europe. The vast majority of these people have no access to regular health care or vaccination programs. This is concerning, as refugees are particularly susceptible to communicable diseases. Exposition to physical and psychological stress, malnutrition, overcrowding, and poor sanitation increases their risk for severe infection [1–3].

The WHO recently stated that health care for the migrating population in Europe should ensure refugees have access to basic medical assessment and, if needed, high-quality health care, without discrimination on basis of gender, age, religion, nationality, race, or legal status [4]. This is particularly important with regard to vaccination services, because insufficient protection against vaccine-preventable diseases (VPD) not only threatens the refugees´ health but can also pose serious risks for host communities. WHO, UNHCR and UNICEF just published a joint technical guidance paper for vaccination of refugees in the European Region [5,6]. As Germany alone has registered more than one million asylum seekers in 2015, there is a strong need for those. However, until today Germany and Europe are struggling to actually implement stringent vaccination standards in daily practice.

As almost no recent data on VPD immunity in the currently migrating population exists, we conducted serological screening for IgG against diphtheria and tetanus (TD) in a large cohort of refugees seeking shelter in six German refugee centers in the summer of 2015.

Material and Methods

Study population

A total of n=801 patients presented to the outpatient clinics of six Northern German reception centers from August 17th to August 26th 2015 for a medical checkup or due to acute complaints. These complaints were mainly common colds or skin diseases like scabies [7]. Routine testing was performed for the following infectious and vaccine preventable diseases: Measles, Mumps, Rubella [8], Hepatitis B [9], Hepatitis C [10], HIV and Syphilis [11]. N=678 (85%) patients were included into serological TD screening, as they reported no vaccination after their arrival in Germany.

Detection of DT seroprevalences

IgG levels for tetanus and diphtheria were assessed by Enzyme Linked Immunosorbant Assay (EIA) according to the manufacturers' recommendations. The laboratory had been certified for routine serological testing according to DIN EN ISO 15189:2014. DT immunity was classified according to manufacturer suggestions. Seroprevalence for tetanus was divided into five subgroups according to manufacturer suggestions:

0. no immune response: 0 IU/ml
1. no secure protection, vaccination needed: 0.01–0.09 IU/ml
2. a secure protection, but vaccination needed: 0.1–0.49 IU/ml
2. bsecure protection, vaccination within two years: 0.5–1.0 IU/ml
3. [3] long-term protection> 1.0 IU/ml

Immune response to diphtheria was divided into four groups:

0. no immune response=0 IU/ml
1. no secure protection, vaccination needed= 0.01–0.09 IU/ml
2. secure protection, but vaccination needed: 0.1–1.0 IU/ml
3. long-term protection > 1.0 IU/ml

Data analysis

All data was extracted from electronic routine patient records and entered by double entry bookkeeping into an electronic database. For personal data protection purposes, all data was anonymized before analysis. Date of birth and gender were kept available for analysis. In n=14 patients, information on gender and in n=43 patients, data on age was unavailable or inconsistent in the records.

Statistics

All statistical analyses were processed using SPSS version 23.0. Calculations of DT seroprevalence were conducted by descriptive statistics. 95% confidence intervals were estimated by bootstrapping (simple, 1000 computations).

Ethics

The Institutional Review Board of Hannover Medical School approved this analysis (# 2972-2015). All patient information was anonymized and de-identified prior to analysis.

Results

The study population consisted of n=678 persons with a median age of 26 years (range 3-76 years). 76.1% of subjects were male, and 23.9% were female. In Figure 1,age and gender distribution of the study population is shown. We observed a clear gender bias within the cohort, with more male refugees in each age group. In all individuals (n=678, 100%), enough serum for successful screening for IgG against tetanus and diphtheria was available.

Tetanus

All subjects screened positive for IgG against tetanus toxoid. However, only 43.7% of tested refugees presented with IgG levels sufficient for long-term tetanus protection (Table 1), and 56.3 % of subjects displayed insufficient tetanus IgG levels and had no secure long-term protection. In 8.7% of tested refugees, short term protection was provided by intermediate anti-tetanus IgG levels, but re-vaccination within the next two years was recommended. In almost half of the subjects (47.7%) immediate boostering of tetanus immunization was necessary due to either low yet protective tetanus IgG levels (19.8% of subjects) or extremely low, non-protective anti-tetanus levels (27.9% of cases).

Diphteria

In the screening for anti-diphtheria toxoid IgG, 23.9% of all refugees in our cohort displayed long-term protective diphtheria IgG levels (Table 2), and (re-) vaccination needed to be performed in the vast majority (76.1%) of cases. Complete seronegativity occurred in 2.1% of tested subjects and almost half of the cohort (45.6% of tested patients) presented with low, unprotective diphtheria IgG levels and needed immediate immunization. In 28.5% of cases, despite short term protective IgG levels, immediate boostering of diphtheria immunization was required.

Age dependent immunity

Next, we studied immunity against tetanus and diphtheria in different age groups of our cohort (Fig. 1). For both diseases, an age-dependent decline in long-term protection was observed. For example,

about 46.2% of children and adolescents and 48.4% of young adults aged 18-24 years were fully protected against tetanus, whereas only 20.6% of refugees above the age of 50 displayed sufficient tetanus IgG levels (Fig. 2A).

The rate of subjects without secure protection against tetanus increased from 25% in underage subjects and 28.8% in young adults to 64.7% in senior refugees (>50 years).

Likewise, 28.8% of children and 26.0% of young adults below the age of 25 were fully immune against diphtheria, but only 14.7% of the old refugees >50 years of age presented with sufficient anti-diphtheria IgG levels (Fig. 2B). Moreover, the rate of subjects without or only with extremely limited diphtheria protection (IgG levels <0.1) displayed an age-dependent increase from 46.1% in children and adolescents and 45.2% in young adults (<24 years) to 61.7% in subjects above the age of 50.

To further corroborate our finding on age-dependent TD immunity, we analyzed disease specific IgG levels in age specific subcohorts. As shown in Figure 3a, highest mean levels of anti-tetanus IgG occurred in young adults between the age of 18 and 34 years. These refugees presented with significantly higher anti tetanus toxoid IgG levels than refugees between 35 and 49 years and subjects above the age of 50 years.

When we analyzed age-dependent anti-diphtheria toxoid IgG levels in the same fashion (Fig. 3B), greatest levels were observed in young adults aged 18-24 years, where IgG levels were significantly higher than in all other age groups.

Although we observed slightly higher tetanus toxoid IgG levels in female refugees and overall higher mean diphtheria toxoid IgG in male subjects, no consistent gender effects on TD immunity were observed in our cohort (Fig. 4)

Discussion

Our work represents the first comprehensive study on TD seroprevalences in a large cohort of refugees coming to Western Europe in the crisis in 2015.

The observed median age of 26 years and the fact that the vast majority (76.1%) of subjects in our cohort was male is in line with current European migration statistics which state that most immigrants coming to Europe during the current crisis are young men [12].

Overall, we found an unsatisfactory rate of protective immunity against TD in the studied population. We observed a rate of 56.3% of refugees without long-term protection against tetanus and 76.1% without long-term immunity against diphtheria, respectively. Overall, 47.7 % of refugees needed immediate initial or revaccination against tetanus, and 45.6% against diphtheria. These results may be explained by poor access to medical care, as the refugees may have only had limited access to regular health care or vaccination programs [1,2].

The WHO recently stated that Europe should ensure that refugees of any gender, age, religion, nationality, race, or legal status have access to basic medical assessment and, if applicable, high-quality health care in their country of destination [4]. This is particularly important with regard to vaccination services against communicable diseases, because insufficient protection against VPD not only threatens a refugee´s health but can also pose serious risks for host communities.

Tetanus still occurs with low frequency in Western countries where mainly elderly patients are affected [13–16]. In developing countries, however, tetanus still is associated with substantial mortality also in neonates and peripartum mothers [17].

In Germany, as in most European countries, vaccinations against tetanus are recommended for all infants with regular boostering. Usually, tetanus-vaccination in childhood is given in combination with diphtheria and pertussis immunization.

The WHO reports a global TD vaccination coverage of 86% in 2014 [18]. Overall vaccination coverage in Germany is around 97%, with a mild age-dependent decline (98% in young adults aged 18-29 vs. 94.9% in subjects aged 70-97 years) [19]. When it comes to decennial booster shots, however, only 75.6% of Germans are properly vaccinated, again with the most dramatic rate of unprotected subjects in oldest age groups (71.1% above the age of 70 years) [20].

Compared to these reports, the observed rate of 56.3% of all refugees in our cohort without long-term tetanus protection, and the frequency of 27.9% of refugees without any secure protection against this life-threatening disease is alarming.

The age-dependent decline of tetanus immunity in our study population was expected, as this finding also occurs in Western communities. In a recent paper on tetanus immunity in Italy, for example, more than 50% of subjects aged 50 years and older had non-protective tetanus IgG levels [14] . However, in our cohort an even more dramatic rate of non-immune subjects aged 50 years and older (64.7%) occurred. Of note, this is particularly concerning because especially elderly patients are at risk for substantial tetanus morbidity and mortality [14,15].

In the pre-vaccination era, diphtheria was associated significant child morbidity and mortality. After introduction of universal vaccination, diphtheria mortality decreased dramatically in the industrialized world [21]. Although incidences are extremely low in Western countries (in the last two decades around 0-0.02 cases/ year in Israel and Slovakia, only one case in Luxemburg), Latvia reported an outbreak of diphtheria in the late 1990ies with 1288 cases of whom 96 patients died [22]. In 2015, one unvaccinated child in Spain died due to a diphtheria infection [23]. During socio-economic crises, diphtheria often re-emerges [21,24]. The European Centre for Disease Prevention and Control reported several cases of cutaneous diphtheria among refugees arriving in Denmark, Germany, and Sweden in 2015 [23].

Diphtheria vaccination regimens vary from country to country. In Germany, a combinatory diphtheria immunization with pertussis and tetanus is recommended for all infants with regular boosters throughout life [25]. In Eastern Europe, diphtheria vaccination coverage is >80-95% [22], and in

Germany, overall coverage is 80% with considerably low rates of vaccinated elderly (e.g. 69.3% in subjects aged 70-79 years) [19]. Recent studies on diphtheria seroprevalence in Western Europe and Israel show that also in countries with good vaccination coverage, the amount of nonprotected subjects (diphtheria IgG < 0.01 IU/ml) increases with age and is between 20 and 50% in adults aged 50 years and older [22], reflecting waning of post vaccination immunity after last booster shots during childhood.

Importantly, the WHO outlined that in order to achieve sufficient herd immunity, diphtheria protection should be at least 90% in children and 75% in adults [26]. By contrast, only 53.9% of all children in our cohort and 53.3% of adults were immune against diphtheria (overall 52.4% of all tested subjects). Although seroprevalences in European residents are also often times also unsatisfactory [22], we should obviously not miss the opportunity to vaccinate incoming refugees presenting with such low immunity rates.

Current German vaccination guidelines recommend boostering all refugees with documented basic immunization against TD that did not receive TD booster shots within the preceding decade [25]. All refugees with uncertain vaccination status should undergo an immediate TD booster [27]. The authors of this paper fully agree with these guidelines and would advocate to, in doubt, rather boost TD vaccination in an individual that is uncertain how long ago exactly last vaccinations were conducted than to miss an opportunity to secure protection against these life-threatening diseases. This is crucial, as reliable information on vaccination status can hardly be obtained from refugees, even on vaccinations received in their host country, as no central database exists. This is especially true for elderly migrants that, in spite of their particularly high morbidity risk, presented with alarmingly low TD seoprevalences in our cohort. As of today, only one case of diphtheria in migrants in Germany 2015 has been reported by the Robert Koch Institute which collects all cases of notifiable infectious diseases in refugees in Germany [28].

One limitation of our analysis may be the fact that we were unable to certainly exclude refugees with prior vaccination during their migration. As we included refugees that presented to the outpatient clinic of their refugee center and reported not to having been vaccinated in Germany, our approach poses the risk to positively select refugees that have a lower threshold to participate in migration healthcare programs. This may have led to an overestimation of protective immunity compared to the general, newly arriving refugee population. Moreover, due to the nature of our current data set, we were unable to decipher subject specific countries of origin. To further evaluate VPD immunity against in refugees entering Europe during the current crisis, nationality specific serological screening for IgG against VDP in a newly arriving, large cohort of refugees will be our next aim.

Health care for the migrating population is an emerging challenge [29–31]. Recently, WHO, UNHCR and UNICEF released a joint technical guidance paper for vaccination of refugees in the European Region [5,6], but as of today no stringent German or European standard that reaches all refugees has been actually implemented in routine care .

With this initial data set, we hope to emphasize the need for fast implementation of stringent vaccination standards for refugees coming to Europe during the current crisis.

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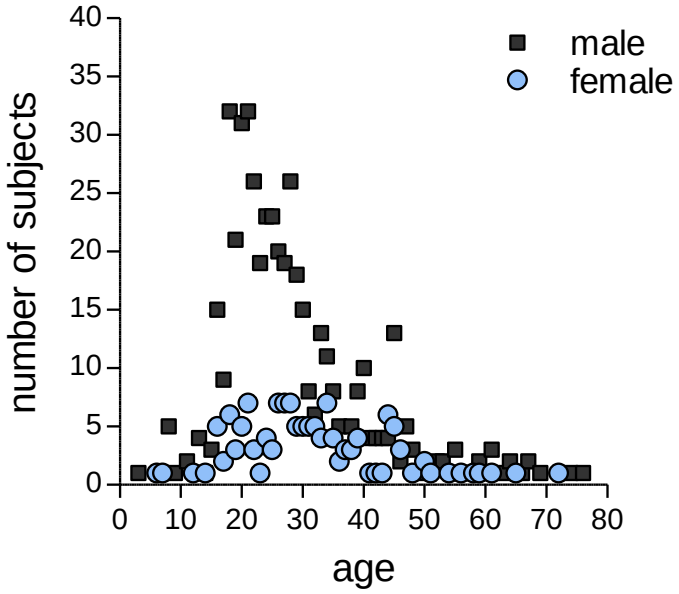

Fig. 1: Age and gender distribution within the cohort. Dots represent male (dark grey checks) and female (light blue circles) subjects within respective age groups (per year).

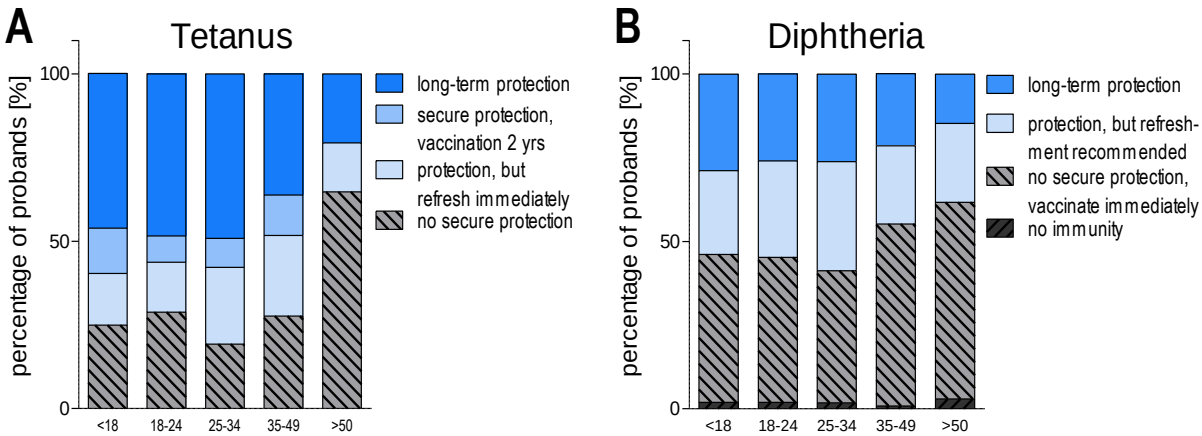

Fig. 2: Age specific immunity for tetanus and diphtheria within the cohort

Graphs display the frequency of subject within the IgG seroprevalences of respective categories for disease specific IgG. A: Tetanus, B: Diphtheria, for colour coding within each bar please check legends next to the graphs.

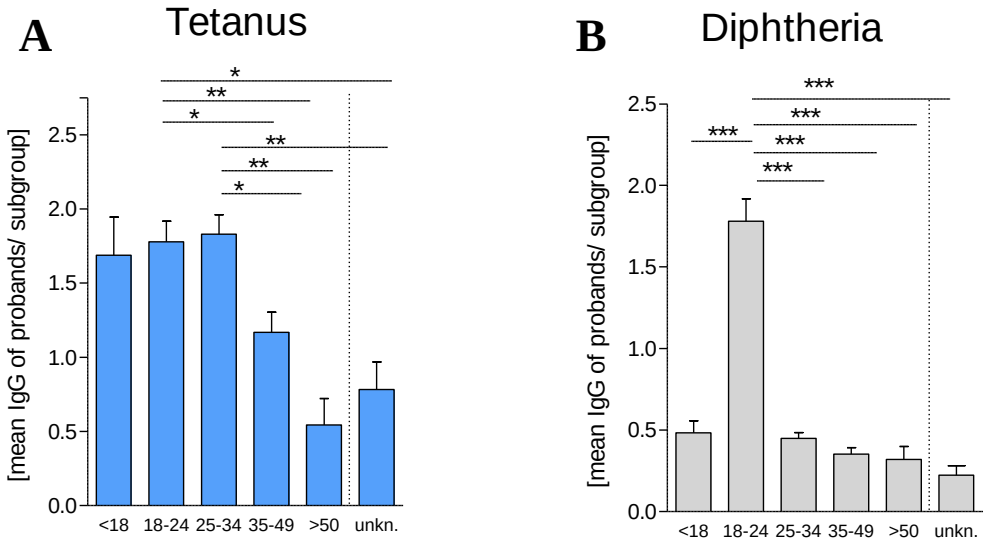

Fig. 3: IgG levels for tetanus and diphtheria in age subgroups of the cohort

Graphs display the specific mean IgG levels of all seronegative and –positive subjects within respective age groups (mean plus standard error mean). A: Tetanus, B: Diphtheria. Bars display mean plus standard error mean, * $p < 0.05$** $p < 0.005$,*** $p < 0.005$ in one way ANOVA testing with Bonferroni correction.

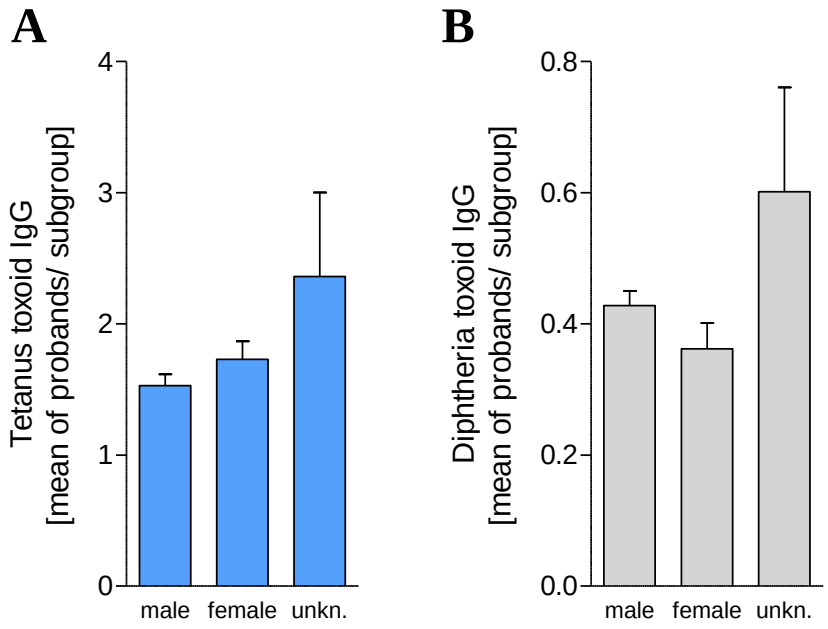

Fig. 4: Gender specific IgG levels for tetanus and diphtheria

Graphs display the specific mean IgG levels of all seronegative and –positive subjects within respective gender groups (mean plus standard error mean). A: Tetanus, B: Diphtheria, Bars display mean plus standard error mean, no significances in in one-way ANOVA testing with Bonferroni correction.

Age range			Tetanus Immunity [IgG levels]							
		0 sero-negative	0.01 – 0.09 no protection, refresh immediately		0.1 – 0.49 protection, refresh immediately		0.5 – 0.99 protection, refresh within 2 years		> 1 long-term protection	
	n	%	%	95% CI	%	95% CI	%	95% CI	%	95% CI
0 – 17	**52**	0	**25.0**	**13.5-38.5**	**15.4**	**5.8-25.0**	**13.5**	**3.9-23.1**	**46.2**	**32.7-59.6**
male	**41**	0	**31.7**	**17.1-46.3**	**17.1**	**7.3-29.3**	**12.2**	**2.4-24.4**	**39.0**	**22-53.7**
female	11	0	**0**	**0**	**9.1**	**0-27.3**	**18.2**	**0-45.5**	**72.7**	**45.5-100.0**
18 – 24	**215**	0	**28.8**	**22.8-34.9**	**14.9**	**10.2-20.0**	**7.9**	**4.7-11.6**	**48.4**	**41.9-55.3**
male	**184**	0	**30.4**	**23.9-37.0**	**15.2**	**10.9-20.7**	**7.1**	**3.8-10.9**	**47.3**	**40.2-54.9**
female	29	0	20.7	6.9-37.9	13.8	3.4-27.6	13.8	3.4-27.6	51.7	31.0-69.0
25 – 34	**218**	0	**19.3**	**14.2-24.8**	**22.9**	**17.9-28.9**	**8.7**	**5.0-12.4**	**49.1**	**42.7-56.0**
male	159	0	23.9	17.6-30.8	23.9	17.6-30.2	10.1	5.7-14.5	42.1	34.6-49.7
female	55	0	7.3	1.8-14.5	20.0	10.9-30.9	5.5	0-12.7	67.3	54.5-80.0
35 – 49	**116**	0	**27.6**	**19.8-35.3**	**24.1**	**16.4-31.9**	**12.1**	**6.0-19.0**	**36.2**	**27.6-44.8**
male	79	0	32.9	22.8-43.0	20.3	12.7-29.1	11.4	5.1-19.0	35.4	24.1-54.6
female	34	0	17.6	5.9-32.4	35.3	20.6-50.0	14.7	5.9-29.4	32.4	17.6-47.1
> 50	**34**	0	**64.7**	**47.1-79.4**	**14.7**	**2.9-26.5**	**0**	**0**	**20.6**	**8.8-35.3**
male	24	0	66.7	45.8-83.3	16.7	4.2-33.3	0	0	16.7	4.2-33.3
female	10	0	60	30.0-90.0	10.0	0-30.0	0	0	30.0	0-60.0
unknown	43	0	41.9	27.9-55.8	25.6	11.6-39.5	4.7	0-11.6	27.9	16.3-41.9
male	29	0	48.3	31.0-65.5	24.1	10.3-37.9	6.9	0-17.2	20.7	6.9-37.9
female	9	0	22.2	0-55.3	22.2	0-55.6	0	0	55.6	22.2-88.9
Total	678	0	**27.9**	**24.5-31.3**	**19.8**	**16.8-23.0**	**8.7**	**6.8-10.9**	**43.7**	**39.7-47.3**
male	516	0	31.6	27.5-35.5	19.4	16.3-23.1	8.7	6.2-11.0	40.3	36.2-44.4
female	148	0	16.2	10.8-22.3	20.9	14.2-27.7	9.5	5.4-14.2	53.4	45.3-61.5
unknown	14	0	14.3	0-35.7	21.4	0-42.9	0		64.3	35.7-85.7

Table 1: Tetanus specific IgG levels in age and gender specific subgroups of the cohort

Percentages and 95% confidence intervals [CI: confidence interval; total includes unknown gender]

Age range		Diphtheria immunity [IgG levels]							
		0 seronegative		0.01 – 0.09 no protection, refresh immediately		0.1 – 0.99 protection, refreshment recommended		> 1 long-term protection	
	n	%	95% CI	%	95% CI	%	95% CI	%	95% CI
0 – 17	**52**	**1.9**	**0-5.8**	**44.2**	**30.8-57.7**	**25.0**	**13.5-36.5**	**28.8**	**17.3-42.3**
male	**41**	**2,4**	**0-7.3**	**46.3**	**31.7-61.0**	**26.8**	**14.6-41.5**	**24.4**	**12.2-39.0**
female	11	**0**	**0**	**36.4**	**9.1-63.6**	**18.2**	**0-45.5**	**45.5**	**18.2-72**
18 – 24	**215**	**1.9**	**0.5-3.7**	**43.3**	**36.3-34.9**	**28.8**	**22.8-34.9**	**26.0**	**20.5-32.1**
male	**184**	**2.2**	**0.5-4.3**	**43.5**	**36.4-50.5**	**26.6**	**19.6-32.6**	**27.7**	**21.2-34.8**
female	29	0	0	41.4	24.1-62.1	44.8	27.6-62.1	13.8	3.4-27.6
24 – 34	**218**	**1.8**	**0.5-4.1**	**39.4**	**33.0-45.9**	**32.6**	**26.6-38.5**	**26.1**	**20.6-32.1**
male	159	1.9	0-4.4	39.0	31.4-47.2	33.3	26.4-40.9	25.8	19.5-32.7
female	55	1.8	0-5.5	40.0	27.3-52.7	32.7	20.0-45.5	25.5	14.5-38.2
35 – 49	**116**	**0.9**	**0-2.6**	**54.3**	**44.8-62.9**	**23.3**	**16.4-31.9**	**21.6**	**13.8-29.3**
male	79	1.3	0-3.8	53.2	41.8-64.5	22.8	13.9-32.9	22.8	15.2-32.9
female	34	0	0	61.8	44.1-76.5	26.5	11,8-41.2	11.8	2.9-23.5
> 50	**34**	**2.9**	**0-8.8**	**58.8**	**41.2-73.5**	**23.5**	**11.8-38.2**	**14.7**	**5.9-26.5**
male	24	4.2	0-12.5	66.7	45.8-83.3	12.5	0-25.0	16.7	4.2-33.3
female	10	0	0	40.0	10.0-70.0	50.0	20.0-80.0	10.0	0-30.0
unknown	43	7.0	0-16.3	55.8	39.5-69.8	27.9	16.3-41.9	9.3	2.3-18.6
male	29	6.9	0-17.2	55.2	37.9-72.4	24.1	7.0-41.4	13.8	3.4-27.6
female	9	0	0	66.7	33.3-100.0	33.3	0 – 66.7	0	0
Total	678	**2.1**	**1.0 – 3.2**	**45.6**	**41.7-49.4**	**28.5**	**25.2-31.9**	**23.9**	**20.5-27.1**
male	516	2.3	1.2-3.7	45.5	41.3-49.8	27.3	23.6-31.0	24.8	20.9-28.7
female	148	0.7	0-2.0	46.6	38.5-54.7	33.8	26.4-41.2	18.9	12.8-25.7
unknown	14	7.1	0-21.4	35.7	14.3-64.3	14.3	0-35.7	42.9	14.3-71.2

Table 2: Diphtheria specific IgG levels in age and gender specific subgroups of the cohort

Percentages and 95% confidence intervals [CI: confidence interval; total includes unknown gender]