High tetanus and diphtheria antitoxin concentrations in Finnish adults—Time for new booster recommendations?

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Abstract

The tetanus and diphtheria vaccination programme in Finland has been running for 50 years. After primary doses, tetanus boosters have been offered to men in military service and decennial boosters recommended for all through the adult life. For 30 years a diphtheria booster was only offered to men in the military service. Not until 1989 diphtheria–tetanus (dT) and diphtheria (d) booster vaccines for adolescence and adults were introduced. In this study serum samples of 990 subjects from 30 years of age, participating in a population survey in 2000–2001, were used to assess the tetanus and diphtheria antitoxin concentrations. More than 70% of the adults up to 50 years of age were fully protected (antitoxin concentrations >0.1 IU/mL) against tetanus and diphtheria. Of these adults more that 76% had antitoxin concentrations >1 IU/mL against tetanus, indicating long-term protection but also an increased risk for hyperimmunisation. A comparison of this study and two immunogenicity studies conducted in Finland in 1987–1988 and 1995–1996 shows the impact of an active decennial dT adult booster programme in a country with a high primary tetanus and diphtheria vaccination coverage in infants since the 1950s. Recommendations for limited decennial boosters by increase the time interval between dT boosters up to 20 years as suggested by this study and also studies performed, e.g., in Denmark and Portugal should be considered. Finnish adults born before 1930 should, however, still be vaccinated with decennial boosters, especially against tetanus.

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1. Introduction

The two main aims of a universal immunisation programme are to prevent the current burden of the target disease and to prepare for possible changes in its epidemiology. The programme has to be efficient in generating immunity as well as be accepted by the citizens. Therefore, the number of doses as well as any adverse events linked to the immunisation need to remain limited. The tetanus (T) and diphtheria (D) immunisation programme for children in Finland has been running for 50 years, starting in 1957. It has consisted of four to five priming doses of DTwP vaccine in the first 4 years of life and a recommendation of a tetanus booster during adolescence, followed by decennial tetanus boosters in adulthood. Between 1943 and 1973, only men in military service were offered the diphtheria booster. Not since 1989, when the diphtheria (d) and diphtheria–tetanus (dT) booster vaccines for adolescence and adults were first introduced, diphtheria vaccine has been recommended for all adults on a decennial basis.

The immunity status of the Finnish population was assessed from samples collected in 1987–1988, before the introduction of...
the new d and dT vaccines [1]. The survey showed that the immune status was poor in the part of the adult population which had had no previous experience of diphtheria outbreaks. Beginning in 1993, diphtheria vaccine has been recommended for travellers and other risk groups due to a diphtheria outbreak which started in the Russian Federation in 1992. A new serosurvey was done in 1995–1996 to measure the impact of these recommendations [2,3]. It was found that the frequent use of diphtheria (d) and diphtheria–tetanus (dT) booster vaccines in the 1990s had a substantial positive effect on the protection of the population against diphtheria.

The coverage of vaccination in Finland is routinely assessed only among infants, and the coverage of tetanus boosters in adults is not directly known. However, data about the distribution of the d and dT vaccines from the National Public Health Institute can be used to estimate the coverage of vaccination in the adult population. In 1993 and 1994 the consumption was approximately 800,000 booster doses per year, corresponding to 22% of the adult population of about 3.5 million people. From 1995 onwards approximately 300,000 dT doses have been distributed annually. These numbers give an estimated coverage of 75%, based on the decennial vaccination recommendation. The use of the d vaccine alone was declining from 35,000 doses in 1995 to below 1000 in 2004, when the product was taken from the market.

The number of reported adverse events linked to dT or d vaccination increased more than two-fold in Finland during the last decade. The relatively constant rate of 80 reports per year between 1997 and 2001 increased to 160 per year in 2002–2003, and to 260 reports per year in 2004–2005. One explanation for the increased rate of adverse events could be improvements in the reporting system, which could also be seen in a slight increase of events reported linked to other vaccinations. It does not, however, explain the more pronounced increase seen after tetanus–dT vaccinations.

Indeed, it has been shown earlier that high pre- and post-vaccination concentrations of tetanus and diphtheria antibodies increase the risk of adverse events after vaccination [4–8]. Especially local reactions, swelling of the lymph nodes and fever, are more common among those with high tetanus antibody concentration [8]. In fact, it is estimated that tetanus antibody concentrations above 5 IU/mL would triple the risk of a reaction to vaccination [9]. Also in Finland, after 50 years of immunisation, the reason for the increase in the number of adverse events may be linked to too high concentrations of pre-vaccination antibodies, especially for tetanus. If this is the case, changes in the decennial booster programme should be considered. The question thus is whether current boosters are too frequent.

When considering the optimal frequency of booster doses it is essential to know the typical duration of immunity. In the case of tetanus and diphtheria, this has been estimated from the half-life of antibodies against the toxoids produced by immunisation. Specifically, the decrease of antitoxin concentrations has been proposed to be exponential, i.e., the log of concentration of antibodies decreases linearly with time. Furthermore, the decrease of tetanus antitoxin concentration has been estimated to be 5–10% per year [10–12]. The pattern of decrease for the diphtheria antitoxin has been shown to be the same as for tetanus [13]. In addition to the decrease in the concentration, also the peak antibody concentration acquired after immunisation is of importance for the duration of protection. The post-booster antibody concentration is higher than after the primary vaccinations, and therefore the duration of protection can be expected to be longer [11].

In order to assess the impact of the diphtheria–tetanus booster programme on antibody concentrations on a population level, a serological survey was carried out. In this paper, we present tetanus and diphtheria antibody concentrations measured from a sample of 990 Finnish adults over 30 years of age. By using a model proposed by Simonsen et al. [11] the relevant antibody concentrations needed for increased time intervals between tetanus boosters is estimated. The impact of the new immunity data compared to data collected earlier in the 1980s and 1990s is discussed.

2. Materials and methods

2.1. Population survey

The National Health 2000 Survey in 2000–2001 [14] was based on a complex sampling design, and together with poststratification weights [15] the results of the analyses is representative with respect to the population. Serum samples from a representative population subsample of 990 subjects, which were randomly selected from the original Health 2000 Survey participants aged 30 years or older, were analyzed for the diphtheria and tetanus antitoxin concentrations. The serum samples were stored in −20 °C before use. The tetanus and diphtheria vaccination status of the subjects was not known.

2.2. Serological assays

Diphtheria and tetanus antitoxins were measured by a double antigen EIA (DAE) developed by Kristiansen et al. [16]. The antitoxin concentrations were calculated with a reference line method using in-house standards calibrated against the two WHO standards containing 120 International Units/mL (IU/mL) of human tetanus antitoxin and 10 IU/mL of equine diphtheria antitoxin, respectively. Geometric mean concentrations (GMCs) were calculated for each antigen and age group. The results are also expressed as proportions of individuals with concentrations ≥1, 0.1–0.9, 0.01–0.09 and <0.01 IU/mL.

Tetanus and diphtheria antitoxin concentrations between 0.01 and 0.1 IU/mL are conventionally considered as low positive, whereas antitoxin concentrations ≥0.1 IU/mL are considered positive. Concentrations ≥1 IU/mL indicate a good long-term protection. The value 0.01 IU/mL is often used as a cut off value indicating protection when functional assays, e.g., the toxin neutralising assay in Vero cells or the DAE assay are used, because a high correlation between these two assays has been shown also in low concentrations [17]. Consequently the value 0.01 IU/mL was used as a cut off value for protection for the results obtained in this study. However, when comparing protection against tetanus in this study and in previous studies done in Finland in the 1980s and 1990s with haemagglutination and indirect Elisa assays, respectively, the value 0.1 IU/mL is used as the cut off level of protection. This is to exclude errors in the interpretation of protection that can occur when different assays are used, especially when levels below 0.1 IU/mL are considered. The corresponding cut off value used for diphtheria is 0.01 IU/mL because the functional Vero cell assay was always used.

2.3. Decline of antibodies

We assume that the rate of decrease of antibody concentration is 0.1/year, i.e., the concentration in an individual decreases 10% per year [11]. If we assume that the protective level is as high as 0.1 IU/mL, the post-booster concentration required for 20 years protection would be approximately 0.74. Individuals with more than 1 IU/mL of tetanus antibodies are thus likely to be protected for at least 20 years.

3. Results

Tetanus antibody concentrations were very high among the younger male and female age groups (Fig. 1A and B). In fact, prac-
Fig. 1. Prevalence (%) of males (A) and of females (B) with protective tetanus antitoxin concentrations in the 2000–2001 survey. Prevalence (%) of males (C) and of females (D) with protective diphtheria antitoxin concentrations in the 2000–2001 survey.

The geometric mean tetanus antitoxin concentration was highest in the male cohort 30–39 years old (5.16 IU/mL) and declined subsequently in the older age groups to 0.06 IU/mL in the cohort ≥70 years of age. The same decline was seen when the female age groups were compared (Table 1). Among the oldest age group aged ≥70, about 50% of the individuals were clearly unprotected (less than 0.01 IU/mL) against tetanus.

The diphtheria concentrations were overall lower than the tetanus concentrations, but the proportion of protected (≥0.01 IU/mL) was more than 90% in all age cohorts below 70 years of age, except 88% in the female age group 50–59 years of age (Fig. 1C and D). The proportion of subjects with antitoxin levels more than 0.01 IU/mL against diphtheria was also high for the elderly men and women ≥70 years of age, 74% and 87%, respectively, due to the fact the older population has experienced diphtheria outbreaks in the 1940s. The proportion of fully protected was however lowest in this age group compared to the younger age groups. Only 47% of the males and 40% of the women ≥70 years of age had antibody concentrations ≥0.1 IU/mL (Fig. 1C and D). The geometric mean concentration varied from 0.50 IU/mL in the youngest male age group to 0.10 IU/mL in the oldest male group (Table 1). The geometric mean concentrations in the female groups were quite similar to those in the male groups.

4. Discussion

A comparison of the immunogenicity studies of tetanus conducted in 1987–1988 and 1995–1996 in Finland and this study from 2000 to 2001 shows that the frequent tetanus boosting in the 1990s had increased the proportion of protected (≥0.1 IU/mL) in the 30–39 age cohort from 84% to 100% already in 1995–1996. In 2000–2001 very high antibody concentrations in adults up to 50 years of age were reached. All individuals below 50 years of age had had the opportunity to receive primary tetanus vaccinations in infancy and a booster dose during adolescence. With a general military service for men in Finland a great majority of males have since 1957 received boosters also at around 20 years of age. If we take into account that a tetanus concentration of 1 IU/mL affords 20 years’ protection, almost the whole cohort of 30–49 years old males and females could well be vaccinated against tetanus again only after year 2020. The currently recommended decennial boosters would not be necessary for these cohorts. In fact, as it is known that high pre-booster antibody concentrations will increase the risk of adverse events after vaccination, they could be harmful.
In the older age groups (≥50 years of age) the anti-tetanus antibody status varied more. The results from the three consecutive seroepidemiological studies show that the proportion of subjects ≥50 years of age protected against tetanus (≥0.1 IU/mL) has first increased from 49% to 54% and then further to 64% in 2000–2001. Of males, over 80% up to 60 years of age have high tetanus antitoxin concentrations (more than 1 IU/mL) affording 20 years’ protection. At the same time, only 40% of the females in the age group 50–59 years of age have high antibody concentrations and every third woman is without protection in the subjects ≥50 years of age.

Men born in the 1940s had taken part to the military service with compulsory tetanus vaccination during the 1960s. In the United States the antitoxin concentrations in male non-veterans is higher than among female non-veterans suggesting that also other reasons may exist behind the difference [18]. One suggested reason is that males have more accidents and thus receive additional tetanus boosters linked to these during their lifetime when compared to females of the same age. It is notable, however, that after 70 years of age half of the individuals, both women and men, would need a booster dose immediately. Based on these serological data, recommendations could be re-tailored so that all individuals between 50 and 70 years of age should get decennial boosters and all over 70 years of age who have not received a booster during the last couple of years should get an immediate DT booster.

The frequent use of diphtheria (d) and diphtheria–tetanus (dT) booster vaccines in the 1990s had a substantial positive effect on the protection of the population against diphtheria. In the 30–39 years age group the proportion of protected (≥0.01 IU/mL) increased from 77% to 92% between the two first studies in the 1980s and 1990s and then to 98% in 2000–2001. The corresponding values for those ≥50 years of age were 60%, 72% and 89%, respectively. Although the proportion of individuals with high diphtheria antitoxin concentrations (≥1 IU/mL) still is lower than that for tetanus for all age groups, the DT booster recommendations based on the tetanus protection levels could also be justified for diphtheria, due to the fact that the proportion of individuals with diphtheria antitoxin concentrations ≥1 IU/mL in the age group 30–49, for which a 20 years interval is proposed, is very high (79–86%) and that the proportion of protected is well above the universally suggested herd immunity threshold of 80–85% [5].

In the United Kingdom all those who have received five doses of tetanus are estimated to have long lasting protection and are thus not recommended to obtain further booster doses unless there is a high risk injury [19]. It has also been suggested that decennial T or dT boosters during adulthood could be replaced by a single booster dose given at the age from 50 to 65 [9,20]. Another way to limit boosters in those who have completed their childhood schedule and especially in those who have high pre-existing concentration of antibodies is to increase the time interval between dT boosters up to 20 years. This latter option is suggested by the present study and also studies performed, e.g., in Denmark and Portugal [11,21]. Additional boosters would be given during wound treatments.

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References