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Immunity to tetanus and diphtheria in the UK in 2009

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ABSTRACT

Introduction: This study aimed to estimate the immunity of the UK population to tetanus and diphtheria, including the potential impact of new glycoconjugatate vaccines, and the addition of diphtheria to the school leaver booster in 1994.
Methods: Residual sera ($n = 2697$) collected in England in 2009/10 were selected from 18 age groups and tested for tetanus and diphtheria antibody. Results were standardised by testing a panel of sera ($n = 150$) to enable comparison with a previously (1996) published serosurvey. Data were then standardised to the UK population.
Results: In 2009, 83% of the UK population were protected (≥0.1 IU/mL) against tetanus compared to 76% in 1996 ($p = 0.079$), and 75% had at least basic protection against diphtheria (≥0.01 IU/mL) in 2009 compared to 60% in 1996 ($p < 0.001$). Higher antibody levels were observed in those aged 1–3 years in 2009 compared to 1996 for both tetanus and diphtheria. Higher diphtheria immunity was observed in those aged 16–34 years in 2009 compared to 1996 (geometric mean concentration [GMC] 0.15 IU/mL vs. 0.03 IU/mL, $p < 0.001$). Age groups with the largest proportion of susceptible individuals to both tetanus and diphtheria in 2009 were <1 year old (>29% susceptible), 45–69 years (>20% susceptible) and 70+ years (>32% susceptible). Low immunity was observed in those aged 10–11 years (>19% susceptible), between the scheduled preschool and school leaver booster administration.
Discussion: The current schedule appears to induce protective levels; increases in the proportions protected/GMCs were observed for the ages receiving vaccinations according to UK policy. Glycoconjugate vaccines appear to have increased immunity, in particular for diphtheria, in preschool age groups. Diphtheria immunity in teenagers and young adults has increased as a result of the addition of diphtheria to the school leaver booster. However, currently older adults remain susceptible, without any further opportunities for immunisations planned according to the present schedule.

1. Introduction

The current UK immunisation policy recommends five doses of tetanus and diphtheria toxoid; an accelerated primary course at ages 2, 3 and 4 months (given as DTaP/IPV/Hib vaccine), followed by booster doses at age 3 years 4 months to 5 years (pre-school booster, DTaP/IPV vaccine) and between 13 and 18 years of age (school leaver booster, Td/IPV vaccine) [1]. Vaccination coverage of primary immunisations evaluated at one and two years has remained at around 91–95% in the UK since the beginning of the 1990s [2]. Assessment of the coverage of the preschool booster started in 1999/2000 and remained stable, between 78% and 82%, during the following decade, before increasing to 86% in 2009/2010. Vaccination coverage of the school leaver booster is unclear (data are collected only as number of doses given). For adults who have completed the five dose schedule there are no scheduled boosters for tetanus and diphtheria. Prior to 2002 a tetanus-containing vaccine was recommended following presentation of a tetanus prone wound if the last tetanus vaccine was received more than ten years previously, although a survey of accident and emergency departments in 2004 found that this practice was still continuing contrary to Department of Health guidance [3]. Currently vaccination should occur following presentation of a tetanus prone injury to health

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services if the patient is not already fully immunised [1]. Opportunities for additional vaccination may occur during a travel health consultation for example for those who are going to live or work in diphtheria epidemic or endemic areas (the same UK policy is also followed by the military), or for occupational reasons (e.g. if working in a microbiology laboratory) [1]. A recent survey of vaccination policies across 29 EU/EEA countries reported that tetanus and diphtheria vaccines are recommended to all adults in 22 and 21 countries respectively although only six countries have data on coverage of tetanus adult boosters, and five on diphtheria coverage [4]. The UK is one of the few European countries where routine adult booster doses are not recommended; other countries may therefore find the UK experience of interest in relation to their own policy.

Clinical cases of either disease are now rare in the UK. Tetanus has occurred mainly in unimmunised older adults [5] with 17/27 cases in the last five years being aged >45 years. A cluster of 25 tetanus cases was reported in 2003/04 among young adult injecting drug users [6] and sporadic cases are occasionally reported in this risk group (three cases in the last five years). Toxigenic *Corynebacterium diphtheriae* infection reported in the UK is usually acquired overseas in countries where the disease is still endemic and is transmitted from person to person via respiratory droplets and close contact [7]. In contrast, toxigenic *Corynebacterium ulcerans* is a zoonotic infection, and although traditionally associated with exposure to cattle, raw milk or dairy products, in recent years has been associated with contact with companion animals [7–10]. Five classic respiratory diphtheria cases were reported in the UK in the last decade, four of whom were aged >45 years.

Since 1992, glycoconjugate vaccines containing tetanus toxoid (TT) or CRM_{197} (a non toxigenic natural variant of diphtheria toxin) carrier proteins have been introduced into routine and catch-up immunisation programmes in the UK (Appendix A). In clinical trials administration of TT or CRM_{197} glycoconjugate vaccines has increased immunity to tetanus or diphtheria respectively [11–13]. In the Netherlands, increased tetanus antitoxin antibody levels have been observed in some age groups following the introduction into the national immunisation programme and catch-up campaign of meningococcal serogroup C glycoconjugate (MCC) vaccine, using TT as the carrier protein [14,15].

In 1994, low dose diphtheria toxoid (d) was added to the school leaving booster in the UK (which previously only contained tetanus and polio vaccine). This action was prompted by the epidemics of diphtheria in eastern Europe and the concern about waning of vaccine induced immunity of adults in the UK. Gaps in immunity have previously been identified in older adults in the UK; in 1996 only 53% and 29% of those aged >60 years were protected against tetanus and diphtheria respectively [16]. Other European countries have also identified lower immunity to tetanus and diphtheria in older adults [17–19].

Given these programme changes since the previous tetanus and diphtheria seroepidemiologic study undertaken in England and Wales in 1996 [16], there is uncertainty about the current immunity profile. Consequently, this study was undertaken to estimate the immunity of the UK population to tetanus and diphtheria, and interpret the findings in order to inform vaccination policy.

2. Methods

2.1. Serum samples

Serum samples representing the entire ranges of age and most geographical regions of the population of England were selected from the Health Protection Agency (HPA) seroepidemiology collection. Briefly, participating NHS and HPA laboratories submit residual sera from routine diagnostic testing to the HPA Seroepidemiology Unit. All samples are anonymised, a unique identity number is assigned and details of age, gender and geographical location are collated on a database. Approximately 150 samples were randomly selected from each of 18 age groups (total $n = 2697$), in order to allow the proportions protected within each age group to be estimated with 95% confidence intervals (CIs) to within ±8%. The majority of samples with valid results had a sample date between January and December 2009 (98%, 2640/2688 for tetanus, 98%, 2641/2689 for diphtheria), with the remainder from January to February 2010.

2.2. Standardisation panel

In addition, a panel of 150 sera (50 selected randomly from each of those which had full, basic protection and susceptible results) from the original 1996 samples were tested using the same multiplexed fluorescent bead assay as the main 2009 serum survey. These results were then used to standardise the 2009 data to enable comparisons with 1996 results. For the 1996 sera, antibody to TT was originally measured by an in house, indirect enzyme linked immunosorbent assay (ELISA) and antibody to diphtheria toxin was measured by a time resolved fluorimetric immunoassay system commonly known as DELFIA (dissociation enhanced lanthanide fluorescence immunoassay) [16].

2.3. Serology

All serum samples were assayed in the Vaccine Evaluation Unit (VEU) at the HPA Public Health Laboratory, Manchester, using a multiplexed fluorescent bead assay to quantify IgG antibodies to tetanus and diphtheria toxoid, based upon previously published methodology [20]. Similar methods have also been used in the VEU to quantify antibodies to meningococcal serogroups A, C, W135 and Y [21] and multiple pneumococcal serotypes [22].

2.4. Data analysis

Standardisation of 2009 data with 1996 data via the selected 1996 panel of 150 sera was conducted using methodology previously described [23]. Panel results from 1996 were plotted against those obtained in 2009 to derive standardisation equations, which were applied to the 2009 quantitative results.

Geometric mean concentrations (GMC) were calculated for each age group for 1996 and 2009, apart from <1 year olds in 1996 as immunity in this age group was not assessed at that time. In addition, GMCs were calculated for males and females separately. Changes in serological profiles by age were interpreted with the aid of 95% CIs on the proportions. For comparison of GMCs for males and females for each age group the Bonferroni correction for multiple comparisons was used, so that only significant differences where $p < 0.0028$ were accepted (0.05/18, since there were 18 age groups).

For tetanus, antitoxin levels <0.1 IU/mL denote susceptibility, antitoxin levels of 0.1–1.0 IU/mL are protective and levels >1.0 IU/mL are considered as giving long term protection as per the previous 1996 study [16,24]. For diphtheria, antitoxin levels <0.01 IU/mL denote susceptibility, antitoxin levels 0.01–0.099 IU/mL provide basic protection, and antitoxin levels ≥0.1 IU/mL are fully protective, as per the international standard [25].

For both the 2009 data and the previous 1996 results, the proportions protected were standardised by age and sex to the 2009 and 1996 UK populations respectively [26]. Although samples were only collected in England, the vaccination schedule applies to the