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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

CLINICAL OVERVIEW

Primary diphtheria immunisation of adolescents and adults with low-dose vaccine, a survey of historic evidence from the literature

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Abstract

The Public Health Agency of Sweden carried out a literature review on diphtheria vaccinations for seronegative people above 6 years of age with an uncertain vaccine history. The aim was to harmonise national Swedish recommendations with the current World Health Organization recommendations. There was no firm conclusion about dosage. Some low-dose vaccines used in the past had suboptimal potency, while others evoked adequate levels of antitoxin after three primary doses. We concluded that low-dose diphtheria vaccines that have been approved by a national medical products agency can be used for primary vaccination against diphtheria for individuals above 6 years of age.

KEYWORDS
diphtheria, low dosage, primary, toxoid, vaccination

Diphtheria-like diseases have been described throughout history, but diphthérite was not used until 1826.[1] The aetiological bacterial agent *Corynebacterium diphtheriae* was identified in 1884 and it became clear that serious clinical symptoms were caused by an exotoxin produced by certain strains of *Corynebacteria*. The diphtheria toxin was characterised 4 years later and the antitoxin was manufactured shortly afterwards and used to prevent and treat symptomatic diphtheria.[1] A requisite for toxin production was that the strain had been infected by a unique bacteriophage.[2]

The fact that the chemically inactivated diphtheria toxoid stimulated immunity to diphtheria, without inducing the disease, was discovered in 1924.[1] Widespread mass vaccination have controlled diphtheria epidemics since the 1930s, but placebo-controlled clinical trials and valid estimates of vaccine efficacy have been lacking. However, some general conclusions can be drawn from systematic evidence from historical outbreaks.[3] Textbooks state that a serum antitoxin level of 0.01 international units (IU)/ml is the lowest level that can provide some degree of protection, 0.1 IU/ml is generally considered protective and 1.0 IU/ml or more may be needed for solid long-term protection. No level provides absolute protection.[4]

Toxoid vaccines against diphtheria and tetanus are the cornerstones of childhood immunisation programmes. The rollout has been so successful that today it is almost impossible to find documented vaccine-naive adult controls for clinical trials.

Sweden's diphtheria vaccinations are regulated by the National Immunization Program and the Communicable Diseases Act (SFS 2004:168). Childhood vaccine coverage has exceeded 97% for 30 years. Boosters are recommended every 20 years, but not consistently provided. The Public Health Agency of Sweden (PHAS) oversees the programme, including the number of doses and dosages needed. Since 2017, there has been a small discrepancy between the national Swedish and World Health Organization (WHO) recommendations for adolescents and adults with uncertain vaccine documentation. The WHO recommends three doses of a low-dose adult type

diphtheria toxoid vaccine for people above 6 years of age without a written vaccine history, to minimise reactogenicity.[5] In contrast, the PHAS recommends that vaccine-naive adolescents and adults should receive three full or infant doses. However, single diphtheria vaccines are not available in Sweden and the PHAS recommends a low-dose diphtheria toxoid vaccine combined with a tetanus toxoid for adults. A sero-surveillance study including 18 European countries demonstrated low overall anti-diphtheria immunoglobulin G levels and the need for improved protection for middle-aged adults.[6]

The aim of this literature review was to see whether PHAS´ recommendations could be modified and aligned with the current WHO recommendations. Studies published up to 31 October 2017 were screened using the PubMed, CINAHL and Scopus databases and the keywords adult, elderly, diphtheria and diphtheria toxoid were combined with immunisation, vaccination or vaccine. The list of the selected studies were screened by at least two people to see whether the papers answered our patient/population, intervention, comparison and outcomes criteria. The question was whether a primary schedule of three low-dose diphtheria vaccinations induced sufficient antibody levels, of at least 0.1 IU/ml, to protect seronegative individuals above 6 years of age. Our confidence in the selected papers were assessed by at least two people as good, fair or poor, using study quality assessment tools from the US National Institutes of Health (detailed data not shown).

The database search identified 3289 papers after duplicates were removed, 78 were assessed for eligibility. The qualitative synthesis comprised six studies, published from 1981 to 2007: five observational studies with low numbers of vaccinated seronegative subjects, ranging from 23 to 72 subjects and a controlled clinical trial with 201 seronegative vaccines.

A meta-analysis was not possible because the studies varied so much in terms of vaccine schedule, dosage and laboratory methods and it was not meaningful to present them in one table. The six studies are discussed individually and we had good confidence in the first three, from the USA,[7] Sweden[8] and Europe.[9]

The USA study, published in 1982, focused on 58 previously unvaccinated members of a rural Amish community in Iowa who received three intramuscular doses of d and t toxoids at 0, 5 and 57 weeks.[7] The vaccine (Connaught Laboratories, Pennsylvania, USA), which is no longer produced, was said to contain 1.5 flocculation units (Lf) of diphtheria toxoid and 5 Lf units of tetanus toxoid. The serum diphtheria antitoxin responses were measured by quantifying skin-necrotising activity in rabbits. A primary immune response was no antibodies detected prior to the first vaccination and no rise in antibody titres after 1 week. Seroconversion was defined as a rise in antitoxin titres to at least 0.01 standard units/ml. The authors reported that 24/24 children and 23/23 adults showed a primary response. All had seroconverted by week 61, but one adult did not attain the 0.1 unit/ml level. The authors concluded that this low-dose vaccine evoked protective levels of antitoxins against diphtheria.[7]

A Swedish study, published in 1989, showed that sero-negative adults who did not respond to their first dose received two more subcutaneous doses of the same diphtheria vaccine. In 38 cases, this was the normal Swedish infant 0.5 ml dose (15 Lf) and in 34 it was half the dose (7.5 Lf), given at zero, two and 10 months. The vaccine (National Bacteriological Laboratory, Stockholm, Sweden), which is no longer produced, had an estimated potency of 2 IU/Lf. Titres of diphtheria antitoxin were assessed by microculture neutralisation in Vero cells. The authors assessed 65/72 subjects and all attained at least 0.01 IU after their third dose. The infant dose group received better protection, with 34/36 (94%) attaining a post-vaccination titre of at least 0.1 IU/ml, compared to 23/29 (79%) in the low-dose group. The authors concluded that primary vaccination with the low-dose vaccine did not induce adequate protective levels of antitoxin in seronegative adults.[8]

The European study of 460 healthy adults in Belgium, the Netherlands and Spain was published in 2007.[9] None had been vaccinated for at least 20 years and they were randomised and vaccinated intramuscularly with one of three different low-dose vaccines at zero, 1 and 6 months. These were said to contain at least 2 IU/dose of diphtheria toxoid and are still used today under trade names such as Boostrix, Boostrix-IPV or Tedivax pro adulto (GlaxoSmithKline Biologicals, Walloon Brabant, Belgium).[9] Antitoxin titres against diphtheria were measured using enzyme-linked immunosorbent assays and, if the value was lower than 0.1 IU/ml after the third dose, the sample was tested again by the more sensitive in vitro neutralisation assay on Vero cells. The exact numbers of seropositive vaccinated subjects before and after each dose were not detailed. However, a graph showed that after one dose, 15%–35% in the different age strata demonstrated a primary seroresponse as they did not attain seroprotective titres against diphtheria. After the third dose, 95%–100% attained solid seroprotective titres of at least 0.1 IU/ml. The authors concluded that three doses of a low-dose diphtheria toxoid vaccine were required to induce seroprotection in subjects with an unknown history of previous vaccinations or who said they had not had diphtheria or tetanus vaccinations.[9]

A Swedish study, published in 1987, had somewhat lower quality. Previously unvaccinated Swedish women, born before 1930 or from 1940 to 1949, received three deep subcutaneous 0.5 ml doses of one of four different investigational diphtheria toxoid vaccines at zero, one and 12 months. The vaccines (National Bacteriological Laboratory) are no longer produced. Two high-dose vaccines contained 6.25 Lf/doses and the other two were more purified and contained 2 Lf/doses. Their estimated potency was approximately 3 IU/Lf. Titres of diphtheria antitoxin were assessed by microculture neutralisation in Vero cells. The highest protected percentage obtained, of at least 0.1 IU/ml, among the vaccinated subjects without a primary seroresponse after dose three, was 29/30 (97%) in the high-dose group and was 28/32 (88%) in the low-dose group. The authors concluded that the low-dose groups were suboptimally protected and that the full dose should be recommended for unprimed adults and infants.[10]

A study from Ukraine published in 2000 also had a somewhat lower quality. Adult factory workers who had not been vaccinated or diagnosed with diphtheria for the last 5 years were recruited in Kyiv,

Ukraine, from 1994 to 1995. They received an adult formulation adsorbed Td from Russia, stated to contain 5 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid per dose. Most vaccinated subjects were given two doses, one at zero days and the second at 30 days. After blood sampling on day seven, a subset were classified with a primary seroresponse of less than 0.005 IU/ml, evaluated by toxin neutralisation in Vero cells. The subjects were scheduled to receive a third vaccine dose on day 425 and be sampled on day 455. The authors reported that 50/488 enrolled subjects had a primary response and most were 40–49 years of age. A third vaccine dose was given to 32/50 and 29/32 had titres above 0.01 IU/ml after that. However, only 20/32 (62.5%) attained 0.1 IU/ml or more. The conclusion was that three doses of this adult low-dose vaccine were suboptimal and did not induce adequate protective titres in unprimed people.[11]

The Australian study was published in 1981, but it was difficult to read and understand, with a significant risk of bias. Investigators recruited non-immune, non-primed Australian students, based on positive Schick tests, and gave them three doses of a reduced 2 Lf dose toxoid vaccine. Dose two was given 4–6 weeks after dose one and dose three was given 3–12 months after dose two. Two different low-dose vaccines (Commonwealth Serum Laboratories, Victoria, Australia), that are no longer produced, were used. Eight university students and six 12-year-old children were tested after dose three and had attained more than 0.1 IU/ml. These were evaluated by an intradermal toxin-antitoxin neutralisation tests in guinea pigs.[12]

Our review method did not produce a firm answer to our defined research question, but the data indicated that some low-dose vaccines could be of suboptimal immunogenicity. This mainly referred to vaccines tested in Ukraine and Sweden that are no longer produced.[8,10,11] Other low-dose vaccines tested in the USA and some European countries were more potent.[7,9]

The most obvious problem with the review was the traditional definition of low-dose or reduced-dose diphtheria toxoid vaccines. Many papers used Lf values for toxoid concentrations to differentiate between low-dose and full-dose vaccines.[4,5] The Lf values indicate the amount of toxoid that could flocculate 1 unit of an international reference antitoxin. There was a general consensus, for historical reasons, that adult vaccines should not contain more than 2 Lf per dose. This reduced the diphtheria toxoid concentration, compared to infant doses, and reduced vaccine reactogenicity, but was sufficiently potent to evoke an antibody response in older children and adults.[4,5]

Today, the flocculation test is considered to provide a good indicator of purity and consistent production. It is a surrogate semi-quantitative marker for toxins and antitoxins without sophisticated laboratory equipment and the need to sacrifice a large numbers of animals.[13] However, the WHO has stated that two toxoid vaccines with the same Lf value can differ considerably in immunising potency and Lf units cannot be used to compare potency between vaccines.[13]

These days it is better to measure vaccine potency in IUs, as determined by guinea-pig challenge assays or by serological assays carried out on either guinea pigs or mice.[5] Vaccine producers use various assays to estimate potency according to different tests required by the WHO, the European Pharmacopoeia and the US Food and Drug Administration.[4] There are still considerable problems comparing vaccines, due to a lack of comparability between laboratories.[14]

In Sweden, every new batch of vaccine has to pass a quality control process, where the vaccine producers' documents are thoroughly evaluated by the Swedish Medical Products Agency. The batch release protocols are not in the public domain. The adult type diphtheria vaccines that are licensed and available in Sweden in 2022 are combined with one or more of the vaccines against tetanus, pertussis and polio. All contain at least 2 IU/dose against diphtheria.

Our review seems to indicate that some low-dose vaccines against diphtheria can be confidently and routinely used above 6 years of age if there is an uncertain vaccine history. It is a requirement that vaccines used for primary vaccination pass the Swedish Medical Products Agency's batch release. The vaccine schedule should preferably follow the ordinary Swedish childhood schedule, with dose two approximately 2 months after dose one and dose three approximately 6–7 months after dose two.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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