A blood agar plate is also inoculated for detection of hemolytic streptococcus. If diphtheria bacilli are isolated, they must be tested for toxin production.

Gram stain and Kenyon stain of material from the membrane itself can be helpful when trying to confirm the clinical diagnosis. The Gram stain may show multiple club-shaped forms that look like Chinese characters. Other *Corynebacterium* species (diphtheroids) that can normally inhabit the throat may confuse the interpretation of direct stain. However, treatment should be started if clinical diphtheria is suggested, even in the absence of a diagnostic Gram stain.

In the event that prior antibiotic therapy may have impeded a positive culture in a suspect diphtheria case, two sources of evidence can aid in presumptive diagnosis: 1) isolation of *C. diphtheriae* from cultures of specimens from close contacts, or 2) a low nonprotective diphtheria antibody titer (less than 0.1 IU) in serum obtained prior to antitoxin administration. This is done by commercial laboratories and requires several days. To isolate *C. diphtheriae* from carriers, it is best to inoculate a Löffler or Pai slant with the throat swab. After an incubation period of 18–24 hours, growth from the slant is used to inoculate a medium containing tellurite.

Medical Management

Diphtheria Antitoxin

Diphtheria antitoxin, produced in horses, was first used in the United States in 1891. It is no longer indicated for prophylaxis of contacts of diphtheria patients, only for the treatment of diphtheria. Since 1997, diphtheria antitoxin has been available only from CDC, and only through an Investigational New Drug (IND) protocol.

Diphtheria Antitoxin

- Produced in horses
- First used in the U.S. in 1891
- Used only for treatment of diphtheria
- Neutralizes only unbound toxin

Antitoxin will not neutralize toxin that is already fixed to tissues, but it will neutralize circulating (unbound) toxin and will prevent progression of disease. The patient must be tested for sensitivity before antitoxin is given. Consultation on the use of diphtheria antitoxin is available through the duty officer at the CDC during office hours (8:00 a.m.–4:30 p.m. ET) at 404-639-3158, or at all other times through CDC's Emergency Operations Center at 770-488-7100.

Persons with suspected diphtheria should be given antibiotics and antitoxin in adequate dosage and placed in isolation after the provisional clinical diagnosis is made and appropriate cultures are obtained. Respiratory support and airway maintenance should also be administered as needed.

Antibiotics

Treatment with erythromycin orally or by injection (40 mg/kg/day; maximum, 2 gm/day) for 14 days, or procaine penicillin G daily, intramuscularly (300,000 U/day for those weighing 10 kg or less, and 600,000 U/day for those weighing more than 10 kg) for 14 days. The disease is usually not contagious 48 hours after antibiotics are instituted. Elimination of the organism should be documented by two consecutive negative cultures after therapy is completed.

Preventive Measures

For close contacts, especially household contacts, a diphtheria booster, appropriate for age, should be given. Contacts should also receive antibiotics—benzathine penicillin G (600,000 units for persons younger than 6 years old and 1,200,000 units for those 6 years old and older) or a 7- to 10-day course of oral erythromycin, (40 mg/kg/day for children and 1 g/day for adults). For compliance reasons, if surveillance of contacts cannot be maintained, they should receive benzathine penicillin G. Identified carriers in the community should also receive antibiotics. Maintain close surveillance and begin antitoxin at the first signs of illness.

Contacts of cutaneous diphtheria should be treated as described above; however, if the strain is shown to be nontoxigenic, investigation of contacts can be discontinued.

Epidemiology

Occurrence

Diphtheria occurs worldwide, but clinical cases are more prevalent in temperate zones. In the United States during the pretoxoid era, the highest incidence was in the Southeast during the winter. More recently, highest incidence rates have been in states with significant populations of Native Americans. No geographic concentration of cases is currently observed in the United States.

Diphtheria Epidemiology

• Reservoir	Human carriers Usually asymptomatic
• Transmission	Respiratory Skin and fomites rarely
• Temporal pattern	Winter and spring
• Communicability	Up to several weeks without antibiotics

Reservoir

Human carriers are the reservoir for *C. diphtheriae* and are usually asymptomatic. In outbreaks, high percentages of children are found to be transient carriers.

Transmission

Transmission is most often person-to-person spread from the respiratory tract. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites).

Diphtheria

5

Temporal Pattern

In temperate areas, diphtheria most frequently occurs during winter and spring.

Communicability

Transmission may occur as long as virulent bacilli are present in discharges and lesions. The time is variable, but organisms usually persist 2 weeks or less, and seldom more than 4 weeks, without antibiotics. Chronic carriers may shed organisms for 6 months or more. Effective antibiotic therapy promptly terminates shedding.

Secular Trends in the United States

Diphtheria was once a major cause of morbidity and mortality among children. In England and Wales during the 1930s, diphtheria was among the top three causes of death for children younger than 15 years of age.

In the 1920s in the United States, 100,000–200,000 cases of diphtheria (140–150 cases per 100,000 population) and 13,000–15,000 deaths were reported each year. In 1921, a total of 206,000 cases and 15,520 deaths were reported. The number of cases gradually declined to about 19,000 cases in 1945 (15 per 100,000 population). A more rapid decrease began with the widespread use of toxoid in the late 1940s.

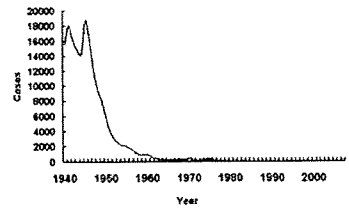
From 1970 to 1979, an average of 196 cases per year were reported. This included a high proportion of cutaneous cases from an outbreak in Washington State. Beginning in 1980, all cases with nontoxigenic cutaneous isolates were excluded from reporting. Diphtheria was seen most frequently in Native Americans and persons in lower socio-economic strata.

From 1980 through 2004, 57 cases of diphtheria were reported in the United States, an average of 2 or 3 per year (range, 0–5 cases per year). Only 5 cases have been reported since 2000.

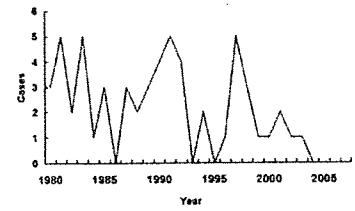
Of 53 reported cases with known patient age since 1980, 31 (58%) were in persons 20 years of age or older; 44% of cases were among persons 40 years of age or older. Most cases have occurred in unimmunized or inadequately immunized persons. The current age distribution of cases corroborates the finding of inadequate levels of circulating antitoxin in many adults (up to 60% with less than protective levels).

Although diphtheria disease is rare in the United States, it appears that *Corynebacterium diphtheriae* continues to circulate in areas of the country with previously endemic diphtheria. In 1996, 10 isolates of *C. diphtheriae* were obtained from persons in an Native American community in South Dakota. Eight of these isolates were toxigenic.

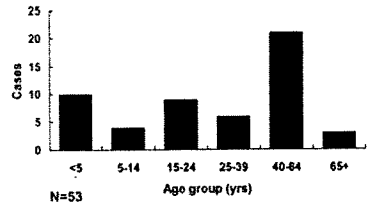
Diphtheria - United States, 1940-2007



Diphtheria - United States, 1980-2007



Diphtheria – United States, 1980-2004
Age Distribution of Reported Cases



None of the infected persons had classic diphtheria disease, although five had either pharyngitis or tonsillitis. The presence of toxigenic *C. diphtheriae* in this community is a good reminder for providers not to let down their guard against this organism.

Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990. By 1994, the epidemic had affected all 15 Newly Independent States (NIS). More than 157,000 cases and more than 5,000 deaths were reported. In the 6 years from 1990 through 1995, the NIS accounted for more than 90% of all diphtheria cases reported to the World Health Organization from the entire world. In some NIS countries, up to 80% of the epidemic diphtheria cases have been among adults. The outbreak and the age distribution of cases are believed to be due to several factors, including a lack of routine immunization of adults in these countries.

Diphtheria Toxoid

Characteristics

Beginning in the early 1900s, prophylaxis was attempted with toxin–antitoxin mixtures. Toxoid was developed around 1921 but was not widely used until the early 1930s. It was incorporated with tetanus toxoid and pertussis vaccine and became routinely used in the 1940s.

Diphtheria toxoid is produced by growing toxigenic *C. diphtheriae* in liquid medium. The filtrate is incubated with formaldehyde to convert toxin to toxoid and is then adsorbed onto an aluminum salt.

Single-antigen diphtheria toxoid is not available. Diphtheria toxoid is available combined with tetanus toxoid as pediatric diphtheria-tetanus toxoid (DT) or adult tetanus-diphtheria (Td), and with both tetanus toxoid and acellular pertussis vaccine as DTaP and Tdap. Diphtheria toxoid is also available as combined DTaP-HepB-IPV (Pediarix) and DTaP-IPV/Hib (Pentacel—see Chapter 14 for more information. Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3 to 4 times as much diphtheria toxoid. Children younger than 7 years of age should receive either DTaP or pediatric DT. Persons 7 years of age or older should receive the adult formulation (adult Td), even if they have not completed a series of DTaP or pediatric DT. Two brands of Tdap are available—Boostrix (approved for persons 10 through 64 years of age) and Adacel (approved for persons 11 through 64 years of age). DTaP and Tdap vaccines do not contain thimerosal as a preservative.

DTaP, DT, Td and Tdap

	Diphtheria	Tetanus
DTaP, DT	7-8 Lf units	5-12.5 Lf units
Td, Tdap (adult)	2-2.5 Lf units	5 Lf units

DTaP and pediatric DT used through age 6 years. Adult Td for persons 7 years and older. Tdap for persons 10-64 years

Diphtheria Toxoid

- Formalin-inactivated diphtheria toxin
- Schedule — Three or four doses + booster
  Booster every 10 years
- Efficacy — Approximately 95%
- Duration — Approximately 10 years
- Should be administered with tetanus toxoid as DTaP, DT, Td, or Tdap

Diphtheria

5

Routine DTaP Primary Vaccination Schedule

Dose	Age	Interval
Primary 1	2 months	—
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
Primary 4	15-18 months	6 months

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
  - –if first dose given at younger than 12 months of age, 4 doses are recommended
  - –if first dose given at 12 months or older, 3 doses complete the primary series

Routine DTaP Schedule for Children Younger Than 7 Years of Age

Booster Doses

- 4 through 6 years of age, before entering school
- 11 or 12 years of age if 5 years since last dose (Tdap)
- Every 10 years thereafter (Td)

Routine Td Schedule for Unvaccinated Persons 7 Years of Age and Older

Dose*	Interval
Primary 1	---
Primary 2	4 weeks
Primary 3	6 to 12 months

Booster dose every 10 years

*ACIP recommends that one of these doses (preferably the first) be administered as Tdap

Immunogenicity and Vaccine Efficacy

After a primary series of three properly spaced diphtheria toxoid doses in adults or four doses in infants, a protective level of antitoxin (defined as greater than 0.1 IU of antitoxin/mL) is reached in more than 95%. Diphtheria toxoid has been estimated to have a clinical efficacy of 97%.

Vaccination Schedule and Use

DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the vaccine of choice for children 6 weeks through 6 years of age. The usual schedule is a primary series of 4 doses at 2,4,6, and 15–18 months of age. The first, second, and third doses of DTaP should be separated by a minimum of 4 weeks. The fourth dose should follow the third dose by no less than 6 months, and should not be administered before 12 months of age.

If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series. If the child was younger than 12 months old when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of four primary DT doses. If the child was 12 months of age or older at the time the first dose of DT was administered, three doses (third dose 6–12 months after the second) completes the primary DT series.

If the fourth dose of DT, DTP or DTaP is administered before the fourth birthday, a booster (fifth) dose is recommended at 4 through 6 years of age. The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Because of waning antitoxin titers, most persons have antitoxin levels below the optimal level 10 years after the last dose. Tetanus toxoid should be given with diphtheria toxoid as Td every 10 years. The first booster dose may be given at 11 or 12 years of age if at least 5 years have elapsed since the last dose of DTP, DTaP, or DT. ACIP recommends this dose be administered as Tdap. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years and older and for adults. A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine and the age these doses were administered. The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above. For unvaccinated persons 7 years and older (including persons who cannot

document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second. For persons 10 years and older ACIP recommends that one of these doses (preferably the first) be administered as Tdap. A booster dose of Td should be given every 10 years. Tdap is approved for a single dose at this time (i.e., it should not be used for all the doses of Td in a previously unvaccinated person 7 years or older). Refer to the pertussis chapter for more information about Tdap.

Interruption of the recommended schedule or delay of subsequent doses does not reduce the response to the vaccine when the series is finally completed. There is no need to restart a series regardless of the time elapsed between doses.

Diphtheria disease might not confer immunity. Persons recovering from diphtheria should begin or complete active immunization with diphtheria toxoid during convalescence.

Contraindications and Precautions to Vaccination

Persons with a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose should not receive additional doses of diphtheria toxoid. Diphtheria toxoid should be deferred for those persons who have moderate or severe acute illness, but persons with minor illness may be vaccinated. Immunosuppression and pregnancy are not contraindications to receiving diphtheria toxoid. See pertussis chapter for additional information on contraindications and precautions to Tdap.

Diphtheria and Tetanus Toxoids Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Moderate or severe acute illness

Adverse Reactions Following Vaccination

Local reactions, generally erythema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria toxoid. Local reactions are usually self-limited and require no therapy. A nodule may be palpable at the injection site for several weeks. Abscess at the site of injection has been reported. Fever and other systemic symptoms are not common.

Exaggerated local (Arthus-type) reactions are occasionally reported following receipt of a diphtheria- or tetanus-containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin 2–8 hours after injections and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid. Persons experiencing these severe reactions usually have very high serum antitoxin levels; they should not be given

Diphtheria and Tetanus Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Fever and systemic symptoms not common
- Exaggerated local reactions (Arthus-type)
- Severe systemic reactions rare

further routine or emergency booster doses of Td more frequently than every 10 years. Less severe local reactions may occur in persons who have multiple prior boosters.

Rarely, severe systemic reactions such as generalized urticaria, anaphylaxis, or neurologic complications have been reported following administration of diphtheria toxoid.

Vaccine Storage and Handling

All diphtheria-toxoid-containing vaccines should be stored continuously at 35°–46°F (2°–8°C). Freezing reduces the potency of the tetanus component. Vaccine exposed to freezing temperature should never be administered.

Suspect Case Investigation and Control

Immediate action on all highly suspect cases (including cutaneous) is warranted until they are shown not to be caused by toxigenic *C. diphtheriae*. The following action should also be taken for any toxigenic *C. diphtheriae* carriers who are detected.

1. Contact state health department or CDC.
2. Obtain appropriate cultures and preliminary clinical and epidemiologic information (including vaccine history).
3. Begin early presumptive treatment with antibiotics and antitoxin. Impose strict isolation until at least two cultures are negative 24 hours after antibiotics were discontinued.
4. Identify close contacts, especially household members and other persons directly exposed to oral secretions of the patient. Culture all close contacts, regardless of their immunization status. Ideally, culture should be from both throat and nasal swabs. After culture, all contacts should receive antibiotic prophylaxis. Inadequately immunized contacts should receive DTaP/DT/Td/Tdap boosters. If fewer than three doses of diphtheria toxoid have been given, or vaccination history is unknown, an immediate dose of diphtheria toxoid should be given and the primary series completed according to the current schedule. If more than 5 years have elapsed since administration of diphtheria toxoid-containing vaccine, a booster dose should be given. If the most recent dose was within 5 years, no booster is required (see the ACIP's 1991 Diphtheria, Tetanus, and Pertussis: *Recommendations for Vaccine Use and Other Preventive Measures* for schedule for children younger than 7 years of age). Unimmunized contacts should start a course of DTaP/DT/Td vaccine and be monitored closely for symptoms of diphtheria for 7 days.
5. Treat any confirmed carrier with an adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks

to ensure eradication of the organism. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of erythromycin and should submit samples for follow-up cultures.

6. Treat any contact with antitoxin at the first sign of illness.

Selected References

CDC. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures. *MMWR* 1991;40 (No. RR-10):1–28.

CDC. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46 (No. RR-7):1–25.

CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(No. RR-3):1–34.

CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and Recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for Use of Tdap Among Health-Care Personnel. *MMWR* 2006;55(No. RR-17):1–33.

Farizo KM, Strebel PM, Chen RT, Kimbler A, Cleary TJ, Cochi SL. Fatal respiratory disease due to *Corynebacterium diphtheriae*: case report and review of guidelines for management, investigation, and control. *Clin Infect Dis* 1993;16:59–68.

Vitek CR, Wharton M. Diphtheria in the former Soviet Union: reemergence of a pandemic disease. *Emerg Infect Dis* 1998;4:539–50.

Vitek CR, Wharton M, Diphtheria toxoid. In Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines.* 5th ed. Philadelphia, PA: Saunders, 2008:139–56.

Immunisation against infectious disease

DH Department of Health
SCOTTISH EXECUTIVE
Llywodraeth Cynulliad Cymru
Wales Assembly Government
DHSSPS
Department of Health, Social Services and Public Safety

Immunisation against infectious disease

Edited by

Dr David Salisbury CB FRCP FRCPCH FFPHM

Director of Immunisation
Department of Health

Dr Mary Ramsay BSc MB BS MRCP MSc MFPHM FFPHM

Consultant Epidemiologist
Health Protection Agency

and

Dr Karen Noakes BSc PhD

Principal Scientist
Immunisation
Department of Health

Published by TSO (The Stationery Office) and available from:

Online
www.tsoshop.co.uk

Mail, Telephone, Fax and E-mail
TSO
PO Box 29, Norwich, NR3 1GN
Telephone orders/General enquiries: 0870 600 5522
Fax orders: 0870 600 5533
E-mail: customer.services@tso.co.uk
Textphone: 0870 240 3701

TSO Shops
123 Kingsway, London, WC2B 6PQ
020 7242 6393 Fax 020 7242 6394
16 Arthur Street, Belfast BT1 4GD
028 9023 8451 Fax 028 9023 5401
71 Lothian Road, Edinburgh EH3 9AZ
0870 606 5566 Fax 0870 606 5588

TSO@Blackwell and other Accredited Agents

Published by The Stationery Office under licence from the Department of Health

Department of Health
Wellington House
133–155 Waterloo Road
London SE1 8UG

First edition 1992
Second edition 1996
Third edition 2006

ISBN-10 0-11-322528-8
ISBN-13 978-0-11-322528-6

Printed in Great Britain by The Stationery Office

N5456496 C1950 11/06

Contents

Acknowledgements

Producing a volume as complex, comprehensive and wide-ranging as this required a huge team effort from many staff at the Department of Health and the Health Protection Agency in particular. First, we would like to thank all those staff who re-drafted the chapters and the individual specialists who contributed their expertise in technical areas. Second, we must thank the members of the Joint Committee on Vaccination and Immunisation who made constructive comments on the drafts and, third, we must give special thanks to those individuals who drew the drafts together into a meaningful whole. These include Judith Moreton, Joanne Yarwood, Dr Dorian Kennedy, Dr Arlene Reynolds, and Chris Owen.

STOP PRESS

Just prior to publication, the World Health Organization published a paper entitled *Temperature sensitivity of vaccines*. See page 23 for more information.

NOTE

This edition reflects policy current at the time of going to press – November 2006
Updates are available at www.dh.gov.uk/greenbook.

Preface

The immunisation programme in the UK continues to evolve, meeting the demand to improve the control of infectious diseases through vaccination. Since the last edition of *Immunisation against infectious disease* (the Green Book), the immunisation programme has seen a number of changes, to both the vaccination schedule and to peoples' attitudes to vaccination. New vaccines have been introduced against meningococcal group C and pneumococcal infections which are the cause of serious diseases. At the same time, as the epidemiology of some diseases changes, certain vaccination schedules have been altered: the school's BCG programme has stopped and a more targeted approach to BCG vaccination has been adopted. Other changes to the immunisation schedule, such as the introduction of a Hib/MenC booster at 12 months of age and the reduction of MenC doses given as a primary course, reflect the importance of diligent surveillance and clinical trials to study the most effective way to use vaccines in the UK schedule.

The Joint Committee on Vaccination and Immunisation (JCVI) continues to play a pivotal role in advising the UK's Health Departments, providing independent scientific advice for the whole programme. JCVI meets three times a year and comprises experts from many areas of medicine and clinical practice especially related to immunisation. The members are independent of government, work to the highest international standards as recognised by the World Health Organization and publish their recommendations and advice, together with those of the various sub-committees, on the Department of Health website.

The objectives of the national immunisation programme include providing clear, evidence-based communications that meet the needs of parents and health professionals, and ensuring that those working in primary care are provided with the support required to implement vaccination programmes effectively.

Following the ill-founded MMR scare, it has become even more important for those working in the field to be able to communicate to parents the benefits of vaccination, the known side effects of vaccines and the safety and efficacy of vaccines to allay fears.

I look forward to the exciting work that lies ahead in developing an immunisation programme that offers safe and effective protection for our children and families both today and in the future.

Andrew J Hall
Chairman, Joint Committee on Vaccination and Immunisation

15

Diphtheria

NOTIFIABLE

The disease

Diphtheria is an acute infectious disease affecting the upper respiratory tract, and occasionally the skin, caused by the action of diphtheria toxin produced by toxigenic *Corynebacterium diphtheriae* or by *Corynebacterium ulcerans*. The most characteristic features of diphtheria affecting the upper respiratory tract are a membranous pharyngitis (often referred to as a pseudo-membrane) with fever, enlarged anterior cervical lymph nodes and oedema of soft tissue giving a 'bull neck' appearance. The pseudo-membrane may cause respiratory obstruction. In the UK, the classical disease is now very rare and clinicians may not recognise it. Milder infections (without toxin production) resemble streptococcal pharyngitis and the pseudo-membrane may not develop, particularly in vaccinated individuals. Carriers may be asymptomatic. Diphtheria toxin affects the myocardium, nervous and adrenal tissues, causing paralysis and cardiac failure.

The incubation period is from two to five days. Patients with untreated disease may be infectious for up to four weeks, but carriers may potentially transmit the infection for longer. Transmission of the infection is by droplet and through contact with articles (such as clothing or bed linen) soiled by infected persons.

In countries where hygiene is poor, cutaneous diphtheria is the predominant clinical manifestation and source of infection. The normal reservoir of *C. ulcerans* is cattle. Infections in humans are associated with the consumption of raw dairy products and contact with animals. Person-to-person spread cannot be ruled out, although it is probably uncommon (Bonnet and Begg, 1999).

There is little likelihood of developing natural immunity from sub-clinical infection acquired in the UK. Based on sero-surveillance studies, approximately 50% of UK adults over 30 years are susceptible to diphtheria. The proportion susceptible increases to over 70% in older age cohorts (Edmunds *et al.*, 2000). High immunisation uptake must be maintained in order to prevent the resurgence of disease which could follow the introduction of cases or carriers of toxigenic strains from overseas.

History and epidemiology of the disease

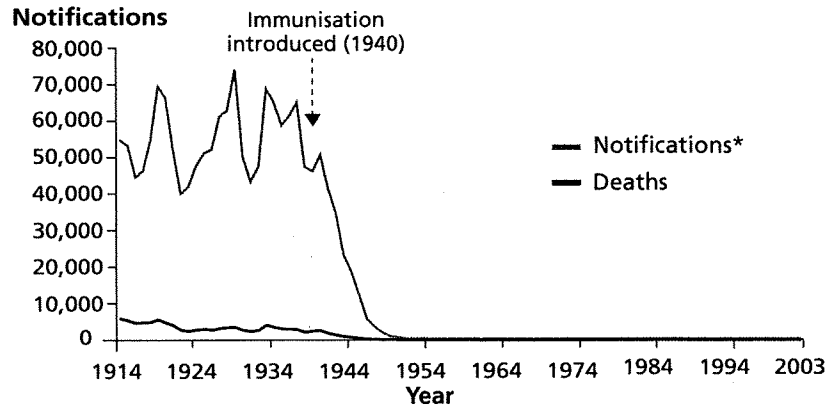
Prior to the 1940s, diphtheria was a common disease in the UK. The introduction of immunisation against diphtheria on a national scale during the 1940s resulted in a dramatic fall in the number of notified cases and deaths from the disease. In 1940, more than 61,000 cases with 3,283 deaths were notified in the UK, compared with 38 cases and six deaths in 1957 (see Figure 15.1).

From 1986 to 2002, 56 isolates of toxigenic *C. diphtheriae* and 47 isolates of toxigenic *C. ulcerans* were identified in England and Wales by the Health Protection Agency (HPA) Streptococcus and Diphtheria Reference Unit (formerly the Public Health Laboratory Service). Of these, eight patients with *C. diphtheriae* infection and six patients with *C. ulcerans* presented with classical pharyngeal diphtheria: the remainder had mild pharyngitis or were asymptomatic. Two deaths from diphtheria occurred between 1986 and 2002: in 1994 an unvaccinated 14-year-old died with a *C. diphtheriae* infection following a visit to Pakistan, and in 2000 an elderly woman died with a *C. ulcerans* infection acquired in the UK.

An increase in notifications of diphtheria since 1992 has been due to a rise in isolations of non-toxigenic strains of *C. diphtheriae* which do not cause classical diphtheria disease (Reacher *et al.*, 2000). These may be associated with a mild sore throat without signs of toxicity.

Diphtheria cases continue to be reported in South-East Asia, South America, Africa and India. A large number of UK citizens travel to and from these regions, maintaining the possibility of the reintroduction of *C. diphtheriae* into the UK. Most cases of diphtheria that have occurred in recent years in the UK have been imported from the Indian subcontinent or from Africa; four cases of cutaneous diphtheria were reported in travellers returning in 2002 (De Benoist *et al.*, 2004). Secondary cases are rare but do occur in the UK.

There was a resurgence of diphtheria in the former Soviet Union, starting with an initial peak in the 1980s and followed by a larger epidemic from 1990 (Dittmann *et al.*, 2000). The epidemic rapidly disseminated, affecting all newly independent states, and peaked in 1994–95. From 1990 to 1998, more than 157,000 cases and 5000 deaths had been reported to the World Health Organization (WHO) (Dittmann *et al.*, 2000). This epidemic was caused by low immunisation coverage in young children, waning immunity in adults and large-scale population movements. Several importations of diphtheria occurred from former Soviet Union countries into Western Europe, including one case into the UK in 1997 (CDR, 1997).



Source: Office for National Statistics; Health Protection Agency
* Notifications up to 1985, laboratory-confirmed cases 1986–2002
† Death data for 2002 are provisional

Figure 15.1 Diphtheria cases and deaths, England and Wales (1914–2003)

The diphtheria vaccination

The vaccine is made from a cell-free purified toxin extracted from a strain of *C. diphtheriae*. This is treated with formaldehyde, which converts it into diphtheria toxoid. This is adsorbed on to an adjuvant – either aluminium phosphate or aluminium hydroxide – to improve its immunogenicity.

Diphtheria vaccines are produced in two strengths according to the diphtheria toxoid content:

- vaccines containing the higher dose of diphtheria toxoid (abbreviated to 'D') contain not less than 30IU
- vaccines containing the lower dose of diphtheria toxoid (abbreviated to 'd') contain approximately 2IU.

Vaccines containing the higher dose of diphtheria toxoid (D) are used to achieve satisfactory primary immunisation of children under ten years of age. Vaccines containing the lower dose of diphtheria toxoid (d) should be used for primary immunisation in individuals aged ten years or over, where they provide a satisfactory immune response and the risk of reactions is minimised. This precautionary advice is particularly pertinent when the early immunisation

history and possibility of past exposure are uncertain. Low-dose preparations are also recommended for boosting (see 'Reinforcing immunisation' section, below).

The diphtheria vaccine is only given as part of combined products:

- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/ *Haemophilus influenzae* type b (DTaP/IPV/Hib)
- diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (dTaP/IPV or DTaP/IPV)
- tetanus/diphtheria/inactivated polio vaccine (Td/IPV).

The above vaccines are thiomersal-free. They are inactivated, do not contain live organisms and cannot cause the diseases against which they protect.

Td/IPV vaccine should be used where protection is required against tetanus, diphtheria or polio in order to provide comprehensive long-term protection against all three diseases.

Monovalent diphtheria vaccine is not available.

Storage

Vaccines should be stored in the original packaging at +2°C to +8°C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

Diphtheria vaccine is only available as part of combined products. It is supplied as a cloudy white suspension, either in a single dose ampoule or pre-filled syringe. The suspension may settle during storage, so the vaccine should be shaken to distribute the suspension uniformly before administration.

Dosage and schedule

- First dose of 0.5ml of a diphtheria-containing vaccine.
- Second dose of 0.5ml, one month after the first dose.
- Third dose of 0.5ml, one month after the second dose.
- Fourth and fifth doses of 0.5ml should be given at the recommended intervals (see below).

Administration

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. This is to reduce the risk of localised reactions, which are more common when vaccines are given subcutaneously (Mark *et al.*, 1999, Diggle and Deeks, 2000; Zuckerman, 2000). However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

Diphtheria-containing vaccines can be given at the same time as other vaccines such as MMR, MenC and hepatitis B. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records.

Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box (UN-approved, BS 7320).

Recommendations for the use of the vaccine

The objective of the immunisation programme is to provide a minimum of five doses of a diphtheria-containing vaccine at appropriate intervals for all individuals. For most circumstances, a total of five doses of vaccine at the appropriate intervals are considered to give satisfactory long-term protection.

To fulfil this objective, the appropriate vaccine for each age group is also determined by the need to protect individuals against tetanus, pertussis, Hib and polio.

Primary immunisation

Infants and children under ten years of age

The primary course of diphtheria vaccination consists of three doses of a D-containing product. DTaP/IPV/Hib is recommended to be given at two, three and four months of age but can be given at any stage from two months to ten years of age. If the primary course is interrupted it should be resumed but not repeated, allowing an interval of one month between the remaining doses.