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The Expanded Programme on Immunization in the European Region of WHO

Diphtheria

Manual for the Management and Control of Diphtheria in the European Region

Copenhagen 1994

ICP/EPI 038 (B)
Distribution: General
Original: English

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Manual for the Management and Control of Diphtheria in the European Region

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ICP/EPI 038 (B)
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EUR/HFA target 5

TARGET 5

REDUCING COMMUNICABLE DISEASE

By the year 2000, there should be no indigenous cases of poliomyelitis, diphtheria, neonatal tetanus, measles, mumps and congenital rubella in the Region and there should be a sustained and continuing reduction in the incidence and adverse consequences of other communicable diseases, notably HIV infection.

Keywords

DIPHTHERIA – Management and control
IMMUNIZATION
EUROPE
CCEE

ACKNOWLEDGEMENTS

I would like to thank Dr Artur Galazka and Professor Sieghart Dittmann for their expert advice in preparing this manual.

BACKGROUND

In 1990, the report of a WHO meeting recommended that a group be set up to produce two manuals for field workers to help eliminate diphtheria. One manual would deal with epidemiological surveillance, management and control of diphtheria; the other would outline procedures for the routine isolation and identification of *Corynebacterium diphtheriae*. The first manual, prepared by Dr Norman Begg of the PHLS Communicable Disease Surveillance Centre, Colindale, London, covers the surveillance, management and control of diphtheria. The laboratory diagnosis of diphtheria is covered in the second manual, which has been prepared by Dr Androulla Efstratiou of the Diphtheria Reference Laboratory, Colindale.

CONTENTS

THE MANAGEMENT AND CONTROL OF DIPHTHERIA

1. INTRODUCTION

Diphtheria is an acute bacterial disease of the tonsils, pharynx, larynx, nose, skin and sometimes the conjunctiva or genitalia. It is caused by *Corynebacterium diphtheriae*, an aerobic gram–positive rod of gravis, mitis or intermedius biotype.

Diphtheria is an ancient disease, which existed in the time of Hippocrates (English 1985). Epidemics were recorded in the sixteenth and seventeeth centuries in Spain, in the eighteenth century in New England and in the nineteenth century in England, Austria, Germany and Denmark. It was described as a clinical entity by Bretonneau in 1826, who named the disease **diphtérite** from the Greek root meaning a skin or hide, because of the leathery appearance of the diphtheritic membrane.

The organism was first cultured by Loeffler in 1884. Within a few years, the work of von Behring, Kitasato and others led to the production of a therapeutic antitoxin, which greatly reduced the mortality from the disease. Active immunisation with diphtheria toxoid was developed during the 1930s, heralding the beginning of the elimination of diphtheria.

2. EPIDEMIOLOGY OF DIPHTHERIA

Man is the only reservoir of diphtheria. The disease is spread by respiratory droplets, mainly from the nose and throat. Cutaneous diphtheria is spread by contact with articles contaminated with discharges from infected lesions. Close face to face contact with a case or a carrier is usually required for transmission to occur. The incubation period is 2 to 5 days, occasionally longer. Untreated patients are infectious for 2 – 3 weeks; antibiotic treatment usually renders patients non–infectious within 24 hours.

Diphtheria is still present in all parts of the world, but is declining in many Regions following the introduction of routine immunisation with diphtheria toxoid. In Europe, widespread immunisation programmes were initiated in the 1940s, and the disease was soon eliminated from many countries. The incidence reached an all–time low in in 1980, when only 623 cases were reported in the Region (figure 1). Since then, two epidemics have occurred, the first in 1982 – 1985 and the second which started in 1990 and is continuing (figure 1). These epidemics mainly affected republics in the former USSR, in particular Russia and the Ukraine (Expanded Programme on Immunization 1993). More than 95% of cases in the European Region are now reported from Russia and the Ukraine.

The current epidemic in Russia started mainly in Moscow and St Petersburg, but is now affecting nearly all regions of the country. The number of cases is continuing to rise: 1,869 cases were reported in 1991, 3,897 cases in 1992 and 15,211 cases in 1993. The incidence in 1993 was 10.2 per 100,000 population. All age groups were affected, although the incidence in children aged 0 – 14 years was about 12 per 100,000, slightly higher than in those aged above 14 years (about 9 per 100,000). Those particularly at risk during the current epidemic include medical staff, public transport employees, homeless people and alcoholics.

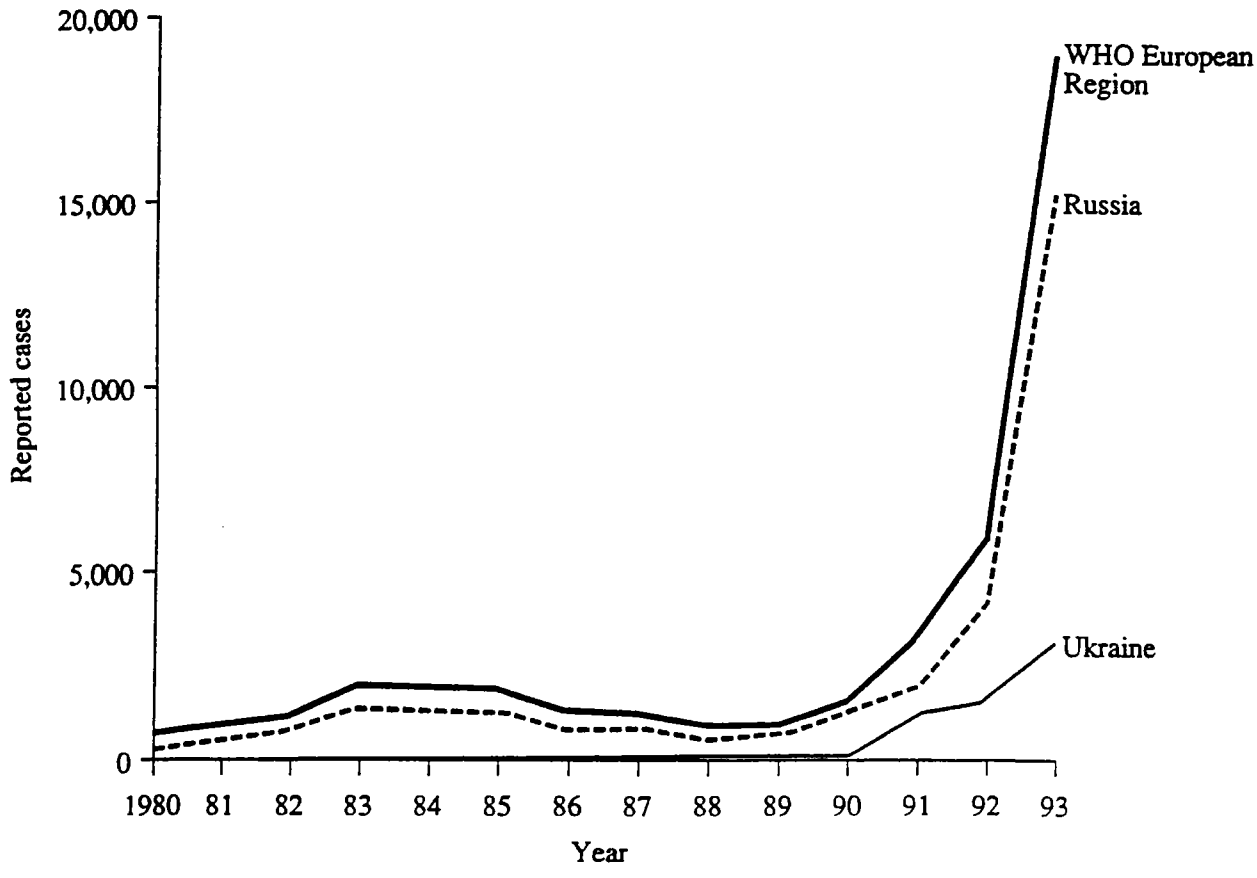


Figure 1. Reported cases of diphtheria in the WHO European Region, Russia and the Ukraine 1980–93

Diphtheria has also re–emerged in other republics of the former USSR, including Azerbeijan (incidence 2 per 100,000 in 1993), Belarus (1 per 100,000), Kazakhstan (0.3 per 100,000), Moldova (0.5 per 100,000), Tajikistan (4 per 100,000) and Uzbekistan (0.2 per 100,000).

The main reasons for the epidemic in Eastern Europe appear to be low vaccine coverage among infants and children, an immunity gap in adults and increasing movement of refugeeand other disadvantaged populations. Additional reasons for the occurrence of country–wide diphtheria epidemics were:

- absence of coordinated and aggressive anti–epidemic measures in many areas, especially mass immunizations in children and adults at high risk
- pediatricians and other physicians were insufficiently aware of the dangers of the disease and of the need for proper diagnosis, case management and management of close contacts
- insufficient information for the general public on the dangers of the disease and the benefits of immunization, and
- last but not least, the lack of vaccine, antisera, and antibiotics in many areas.

In other European countries, diphtheria is mainly a sporadic disease of adults. Most cases are imported from the tropics, although in 1992 and 1993 cases investigated in Bulgaria, Poland, Norway, Estonia, Latvia, Lithuania and Germany were epidemiologically linked to cases in the former USSR. Sixty nine cases were reported in Turkey in 1993. Limited indigenous transmission does occur from time to time. During the 1980s, small outbreaks of diphtheria were reported in Sweden, Germany and Portugal. The Swedish outbreak, from 1984 to 1986, occurred in alcohol and drug abusers. Seventeen cases of clinical diphtheria and 65 carriers were identified (Rappuoli et al 1988).

3. ELIMINATION TARGETS IN EUROPE

3.1 MORBIDITY TARGET

The target for European member states is the elimination of indigenous diphtheria by the year 2000. This means absence of indigenous cases caused by toxigenic *Corynebacterium diphtheriae* strains. Eradication (removal of the causal agent) is not considered possible at present, because there is uncertain evidence that vaccination with diphtheria toxoid can completely eliminate the carrier state.

Elimination of diphtheria should be possible. Man is the only reservoir, the disease is seasonal and thus lends itself to outbreak control, and diphtheria toxoid is safe and effective. There are, however, obstacles to elimination. The immunity gained from vaccination is not life–long and wanes unless boosted (Simonsen et al 1987). Serological surveys have demonstrated gaps in immunity to diphtheria, particularly in adult populations (Christenson and Bottiger 1986, Masterton et al 1987, Galazka and Kardymowicz 1989). An asymptomatic carrier state can exist, even in vaccinated populations. The disease is readily misdiagnosed in countries with a low incidence.

3.2 OPERATIONAL TARGETS

In order to achieve elimination, a number of operational targets were proposed in 1992 by a WHO expert group. These are summarised below:

3.2.1 Coverage

a) By 1995, every country in the Region should achieve 95% coverage of the primary course (DPT3) by 2 years of age.
b) No district in any country to have less than 90% coverage for the primary course at 2 years of age by 1997.
c) By 1995, every country should include a booster dose (booster doses) of a diphtheria–containing vaccine in school age (5–14 years) children and achieve either 95% coverage for this dose or an immunity rate of 90% as determined by appropriate serological studies.

3.2.2 Surveillance

a) By 1994, all countries should have effective diphtheria surveillance to ensure that every case is identified, and access to laboratories to differentiate toxigenic from non–toxigenic strains
b) By 1995 all reported cases of diphtheria should be classified as indigenous or imported.
c) By 1995 the diphtheria immunity status of the adult population should be assessed in all countries by appropriate serological studies.

3.2.3 Outbreak response

The occurrence of a single case requires immediate control measures, such as treatment and isolation of the case, and vaccination and chemoprophylaxis of contacts. During an outbreak, special measures may need to be taken including mass immunization.

Outbreak measures against diphtheria are described in detail in sections 5 and 6 of this manual and a summary is presented in figure 2 (page 13).

4. SURVEILLANCE

The purpose of surveillance is to provide information on which appropriate preventive action can be taken. Four major indicators may be used to monitor progress towards diphtheria elimination:

- Disease incidence
- Immunisation coverage
- Population immunity
- Circulating toxigenic *C. diphtheriae.*

4.1 CLINICAL DIAGNOSIS OF DIPHTHERIA

Diphtheria is now so rare that most physicians have never seen a case. In order to assist physicians to recognise diphtheria, clinical guidelines, accompanied by illustrative photographs should be drawn up and circulated widely. Guidelines should be available as posters and leaflets in physicians' surgeries, child health clinics, casualty departments and other settings where cases of diphtheria may present.

For clinical purposes it is convenient to classify the disease in accordance with the anatomical location of lesions. The following types of diphtheria occur: (1) tonsillar (faucial), (2) pharyngeal, (3) laryngeal or laryngotracheal, (4) nasal, and (5) nonrespiratory, including skin wounds and conjunctival, otic and genital lesions.

Classical respiratory diphtheria is characterized by insidious onset, and membranous pharyngitis with low–grade fever. Although not always present, the membrane is typically gray or white in color, smooth, thick, fibrinous, and firmly adherent (figure 3; page 18). The membrane's extent may vary from a small patch on one tonsil to extensive involvement of both tonsils, uvula, soft palate and pharyngeal wall. The throat is moderately sore in faucial or pharyngotonsillar diphtheria, with cervical lymph nodes somewhat enlarged and tender; in severe cases, there is marked swelling and oedema of the neck. Laryngeal diphtheria is characterized by gradually increasing hoarseness and stridor and most commonly occurs as an extension of pharyngeal involvement in children. Nasal diphtheria, usually mild and often chronic, is marked by unilateral or bilateral nasal discharge which is initially serous and subsequently becomes serosanguineous. The incubation period of diphtheria is usually two to five days but may occasionally be longer.

Presumptive diagnosis is based on observation of the presence of a membrane, especially if extending to the uvula and soft palate, in association with tonsillitis, pharyngitis or cervical lymphadenopathy, or a serosanguinous nasal discharge.

In most cases the cardiac manifestations appear during the second week of the disease. The more extensive the local lesion and the more delayed the institution of antitoxin therapy, the more frequently myocarditis occurs. The late effects of diphtheria appear after 2 – 6 weeks. They include cranial and peripheral nerve palsies and myocarditis (which may occur both in early as well as in later phases of the disease), and are often severe. The manifestations of neuritis appear after a variable latent period, are predominantly bilateral with motor rather than sensory involvement and usually resolve completely. Soft–palate paralysis is the most common manifestation of diphtheritic neuritis. It occurs during the third week and is characterized by a nasal quality to the voice and nasal regurgitation. Other neuritic manifestations include ocular palsy (paralysis of the muscles of accomodation, causing blurring of vision) and paralysis of the diaphragm and limbs (often indistinguishable from Guillain–Barré syndrome). Case fatality rates have changed little in 50 years at 5% – 10%.

Diphtheria should be suspected in the differential diagnosis of bacterial and viral pharyngitis, Vincent's angina, infectious mononucleosis, oral syphilis and candidiasis. The diagnosis is confirmed by bacteriologic examination of lesions.

4.2 REPORTING OF DIPHTHERIA

4.2.1 Reporting to local health authorities

It is essential that *all* suspected cases of diphtheria are rapidly identified and properly investigated. Diphtheria is notifiable in all countries of the Region. A standard case report form should be used for immediate reporting of suspected, probable and confirmed cases to the responsible local health authorities.

4.2.2 Reporting to regional and national health authorities and to the WHO Regional Office for Europe

Depending on the epidemiological situation, national health authorities should decide on the rules for reporting (suspected and/or confirmed cases included, immediate or weekly or monthly reporting) within the different levels of the health service system.

All confirmed cases should be classified as indigenous or imported (infection acquired abroad). All confirmed cases should be reported monthly to the WHO Regional Office for Europe. 'Zero' reports should be made.

Any outbreak including two or more epidemiologically linked confirmed cases should be reported immediately to the national health authority and to WHO.

4.2.3 Surveillance supplementary reporting

Because the disease is rare, many physicians do not appreciate the importance of reporting. It may therefore be necessary to supplement the reporting system with active surveillance in order to detect all cases. This can be done in a number of ways:

- systematic review of all laboratory reports of *C. diphtheriae* to ensure that strains are forwarded to the national reference laboratory for confirmation and toxigenicity testing.
- regular review of hospital records to identify missed cases.
- review of death certficates

4.3 CASE DEFINITIONS

Cases should be classified as suspected, probable or confirmed. Confirmed cases should be classified as indigenous or imported (infection acquired abroad). The following case definitions should be used in classifying cases:

Suspected case
- laryngitis *or* nasopharyngitis *or* tonsillitis

plus
- pseudomembrane

Probable case
- suspected case

plus
- one of the following:
  - recent (< 2 weeks) contact with a confirmed case
  - diphtheria epidemic currently in the area
  - stridor
  - swelling/oedema of neck

– submucosal or skin petechial haemorrhages
– toxic circulatory collapse
– acute renal insufficiency
– myocarditis and/or motor paralysis one to six weeks after onset.
– death

Confirmed case

- probable case

plus

- isolation of a toxigenic strain of *C. diphtheriae* from a typical site (nose, throat, skin ulcer, wound, conjunctiva, ear, vagina)
  or fourfold or greater rise in serum antitoxin, but **only** if both serum samples were obtained before the administration of diphtheria toxoid or antitoxin

Note: Demonstration of toxin production is recommended but not required in typical cases. Microscopic examination of a direct smear of a clinical specimen is **not** sufficiently accurate to substitute a culture.

N.B. Disease caused by *Corynebacterium ulcerans* and non–toxigenic *C.diphtheriae* is excluded from this case definition.

4.4 IMMUNISATION COVERAGE

Coverage in children should be assessed at local and national level using methods recommended by WHO (e.g. using reported data or results of coverage surveys).

Coverage assessment should be performed separately for the primary series of diphtheria–toxoid–containing vaccines (usually DPT) in infants, and for revaccination doses of DT or Td vaccines in older persons. For the primary series, the denominator should be the resident target population and the numerator the number of completed courses (third dose) administered. Coverage should be assessed in children aged 24 months or younger. The assessment should be at least once a year.

4.5 POPULATION IMMUNITY

To achieve elimination, a minimum immunity rate of 90% in children and 75% in adults is required. Periodic serological surveys should be carried out, paying particular attention to adults over 30 whose immunity has not been boosted by natural infection.

For epidemiological purposes the minimum protective level is considered to be 0.01 IU/ml of diphtheria antitoxin in a serum sample (see laboratory manual). The higher level of 0.1 IU/ml is desirable for individual protection. However, in most people it cannot be easily maintained over a long period of time.

Laboratory procedures for measuring antibodies should be adjusted to the WHO reference antitoxin serum (see laboratory manual).

5. CASE MANAGEMENT

The guidelines in this manual are based, with a few exceptions, on those published recently by Farizo and colleagues (1993), the American Academy of Paediatrics (1994) and the American Public Health Assocation (1990).

5.1 HISTORY AND EXAMINATION

The following information should be obtained from the case (see also the laboratory manual):

Patient details	Name, age, sex Address of residence (and of nursery or kindergarden if applicable) Hospital where admitted Physician caring for patient
Laboratory details	Source of specimen(s) Date(s) collected
Clinical details	Symptoms Onset date Treatment – antibiotics – antitoxin
Epidemiological information	Immunisation status Recent travel history List of contact persons including day–care centres and kindergardens

Clinical examination

The clinical examination should include temperature measurement, palpation of cervical lymph nodes and inspection of the pharyngeal wall, tonsils, uvula and nasal antrum for the presence of a membrane. Wounds and other skin lesions should be carefully looked for, as these lesions can disseminate disease.

5.2 LABORATORY INVESTIGATION

Throat and nasopharyngeal swabs should be taken for culture before antibiotic treatment is started. If a membrane is present, samples should be obtained from the membrane or beneath its edge. Any wounds or skin lesion should also be swabbed. A full description of methods for specimen collection is shown in an appendix of the laboratory manual.

A serum sample should be obtained before administration of antitoxin for measurement of antibodies to diphtheria toxin, as demonstration of a non–protective level (< 0.01 IU/ml) may support the diagnosis if cultures are negative.

5.3 TREATMENT

Bacteriological examination may take several days. If diphtheria is strongly suspected, specific treatment with antitoxin and antibiotics should be initiated immediately while bacteriological investigations are still pending. Antitoxin therapy (see below) is still the mainstay of treatment; antibiotic therapy is also required to eradicate the organism and prevent spread.

5.3.1 Diphtheria antitoxin

Diphtheria antitoxin is hyperimmune serum produced in horses. Antitoxin will only neutralize circulating toxin that is not yet bound to tissue, thus prompt administration is critical. Delayed administration increases the risk of late effects such as myocarditis and neuritis.

Before antitoxin is administered, the patient should be tested for sensitivity to horse serum and if necessary, desensitized. The dose of antitoxin to be administered depends upon the site and extent of the diphtheritic membrane, the degree of toxicity and the duration of illness. The following table indicates the suggested dose range for various clinical situations (according to Krugman et al 1992). This scheme is widely used in many countries of the world. However, there may be variations recommended by manufacturers of antitoxin and national health authorities:

Table. Dosage of antitoxin recommended for various types of diphtheria

Type of diphtheria	Dosage (units)	Route
Nasal	10 000 – 20 000	Intramuscular
Tonsillar	15 000 – 25 000	Intramuscular or intravenous
Pharyngeal or laryngeal	20 000 – 40 000	Intramuscular or intravenous
Combined types or delayed diagnosis	40 000 – 60 000	Intravenous

If acute anaphylaxis develops, intravenous epinephrine (0.2 to 0.5 ml of 1:1000 solution) should be administered immediately by intravenous injection.

Antitoxin is probably of no value for cutaneous disease, although some authorities use 20,000 to 40,000 units of antitoxin because toxic sequelae have been reported (American Academy of Paediatrics 1994). Vigorous cleaning of the wound with soap and water and administration of antibiotics (see below) is recommended.

5.3.2 Antibiotics

Antibiotic treatment is necessary to eliminate the organism and prevent spread; it is **not** a substitute for antitoxin treatment. The antibitiotics of choice are erythromycin or penicillin. The recommended dose regimens are as follows:

Penicillin, preferably intramuscular procaine penicillin G (25 000 to 50 000 units/[kg/d] for children and 1.2 million units/d for adults, in two divided doses) or parenteral erythromycin (40 – 50 mg/[kg/d], with a maximum of 2 g/d until the patient can swallow comfortably, at which point erythromycin in four divided doses or oral penicillin V (125 – 250 mg four times daily) may be substituted.

Antibiotic treatment should be continued for 14 days.

5.4 REPORTING

All cases (suspected, probable and confirmed) should be reported immediately, by telephone to the local health authority (see also 4.2). The advice of the national communicable disease surveillance unit and the reference laboratory should also be sought at this stage.

5.5 ISOLATION

The patient should be nursed in strict isolation until bacteriological clearance has been demonstrated by negative cultures of nasopharyngeal and throat swabs obtained at least 24 hours after completing treatment.

All articles in direct contact with the patient and articles soiled by discharges from the patient should be disinfected while the patient is in isolation.

5.6 IMMUNIZATION

Clinical diphtheria does not necessarily confer natural immunity. Patients with diphtheria should therefore be vaccinated before discharge from hospital. Previously unvaccinated individuals should receive immediately a dose of a diphtheria–toxoid–containing vaccine (preferably Td) and complete later a full primary course of not less than three doses. Partially vaccinated persons should complete the primary course according to the nationally recommended schedule; fully vaccinated persons should receive a booster dose unless the most recent dose was given within the past 5 years in which case the booster is unnecessary.

5.7 IDENTIFICATION AND MANAGEMENT OF CLOSE CONTACTS

5.7.1 Definition of close contacts

Anyone who has been in close contact with a case of diphtheria caused by toxigenic *C. diphtheriae* in the previous *seven* days should be considered at risk. Contacts of cases due to non–toxigenic *C. diphtheriae* or *C.ulcerans* (including toxigenic *C.ulcerans*)are not at risk. Close contacts include the following:

- Household members
- Friends, relatives and caretakers who regularly visit the home
- Kissing/sexual contacts
- School classroom contacts
- Those who share the same room at work
- Health care staff exposed to oropharyngeal secretions of the case

5.7.2 Clinical surveillance

All close contacts (as defined above) should be clinically assessed for symptoms and signs of diphtheria and kept under daily surveillance for seven days from the date of the last contact with the case. The daily surveillance should include inspection of the throat for the presence of a membrane and measurement of temperature. Close contacts should be given penicillin, preferably a single dose of intramuscular benzathine penicillin.

The immunisation status should be assessed. For details of antibiotic prevention and immunization in close contacts see below under 5.7.4 and 5.7.5.

5.7.3 Laboratory investigations

Carriage rates of toxigenic *C. diphtheriae* among household contacts of cases may be as high as 25%. It is important to identify asymptomatic carriers because they may transmit the organism. In addition, finding a carrier among close contacts may support the diagnosis of diphtheria in the absence of bacteriologic confirmation. In the search for cases and carriers, nasal and pharyngeal swabs should be obtained from all close contacts, regardless of vaccination status. Contacts should also be examined for the presence of wounds or skin lesions. Any such lesions should be swabbed, as they can act as a source of infection.

Note: The risk of infection is directly related to the closeness and duration of contact. The search for infected contacts should be limited to circumstances in which intimate respiratory or physical contact may have occurred. Wider studies for carriers are time–consuming, expensive and counterproductive.

If a positive culture from a close contact is obtained the following measures should be undertaken:

- carriers should avoid close contact with inadequately vaccinated persons;
- identify close contacts of carriers and proceed with preventive measures described for close contacts of a case. Preventive measures to close contacts of carriers are important but should be considered a lower priority than control measures for contacts of a case.
- repeat culture a minimum of two weeks after completion of antibiotics to assure eradication of the organism. Persons who continue to harbour the organism after treatment with either penicillin or erythromycin should receive an additional 10–day course of oral erythromycin and should submit samples for follow up cultures.

5.7.4 Antibiotics

The recommended regime for use in close contacts is:

A single dose of intramuscular benzathine penicillin (600 000 units for children < 6 years of age and 1.2 million units for persons > 6 years of age); or

A 7 to 10–day course of erythromycin (40 mg/[kg/d] for children and 1g/d for adults), is an acceptable alternative, but is not routinely recommended because of poor compliance.

Culturing may be repeated after antibiotic prevention.

5.7.5 Immunization

All close contacts who have received less than three doses of diphtheria toxoid in the past, or whose immunization status is unknown, should be given an immediate booster dose of diphtheria toxoid–containing vaccine, then complete the full immunization series according to the nationally recommended schedule. Contacts who have had three doses of vaccine in the past should also receive an immediate booster dose, unless the last dose was given in the previous twelve months, in which case a booster dose is unnecessary.

The measures for the management of cases and close contacts of diphtheria are summarised in figure 3.

6. OUTBREAK MANAGEMENT

The ultimate responsibility for **planning and coordination** of diphtheria outbreak control operations should rest with a '(National or Regional) Committee on Diphtheria Control' chaired by the Minister of Health (or the Chief Public Health Officer of the region affected) and consisting of persons representing services that have to play an active role during the epidemic as well as appropriate experts. Whilst the Committee should be as small as is practicable, depending on the administrative organization of the country concerned, membership of the committee may need to consider representation from, for example:

- senior officials of the public services, e. g.finance, transport, communications, police, armed forces;
- health service staff, e.g. specialists in immunization, epidemiological surveillance, infectious disease medicine, paediatrics, microbiology
- pharmacists responsible at national (or regional) level for supply of vaccines, drugs etc.
- the media;
- representatives of the regions (districts) mostly affected, and
- in large outbreaks, on ad hoc basis international organizations (WHO, UNICEF, UNDP), governmental and non–governmental organizations (e.g. USAID, IFRC, MSF, CDC).

The '(National or Regional) Coordinator for the Control of Diphtheria' (see below) should act as the secretary of the ' Committee on Diphtheria Control'.

The health service specialists working as members of the committee should prepare the decisions of the committee, in close collaboration with the secretary.

The **'(National or Regional) Coordinator for the Control of Diphtheria'**: Based on the decisions of the '(National or Regional) Committee on Diphtheria Control', at national or regional level, the responsibility for **implementing** diphtheria control operations should rest with a single individual in the health service, identified by title, e.g. 'Coordinator for the Control of Diphtheria'. The coordinator appointed should be a physician of recognized competence and his authority and responsibilities should be clearly defined. His field of competence should cover as much as possible of the following: management experience, epidemiology of infectious diseases, relevant aspects of infectious disease medicine and laboratory diagnosis.

The coordinator should be supported by appropriate staff recruited within the national administrative structure.

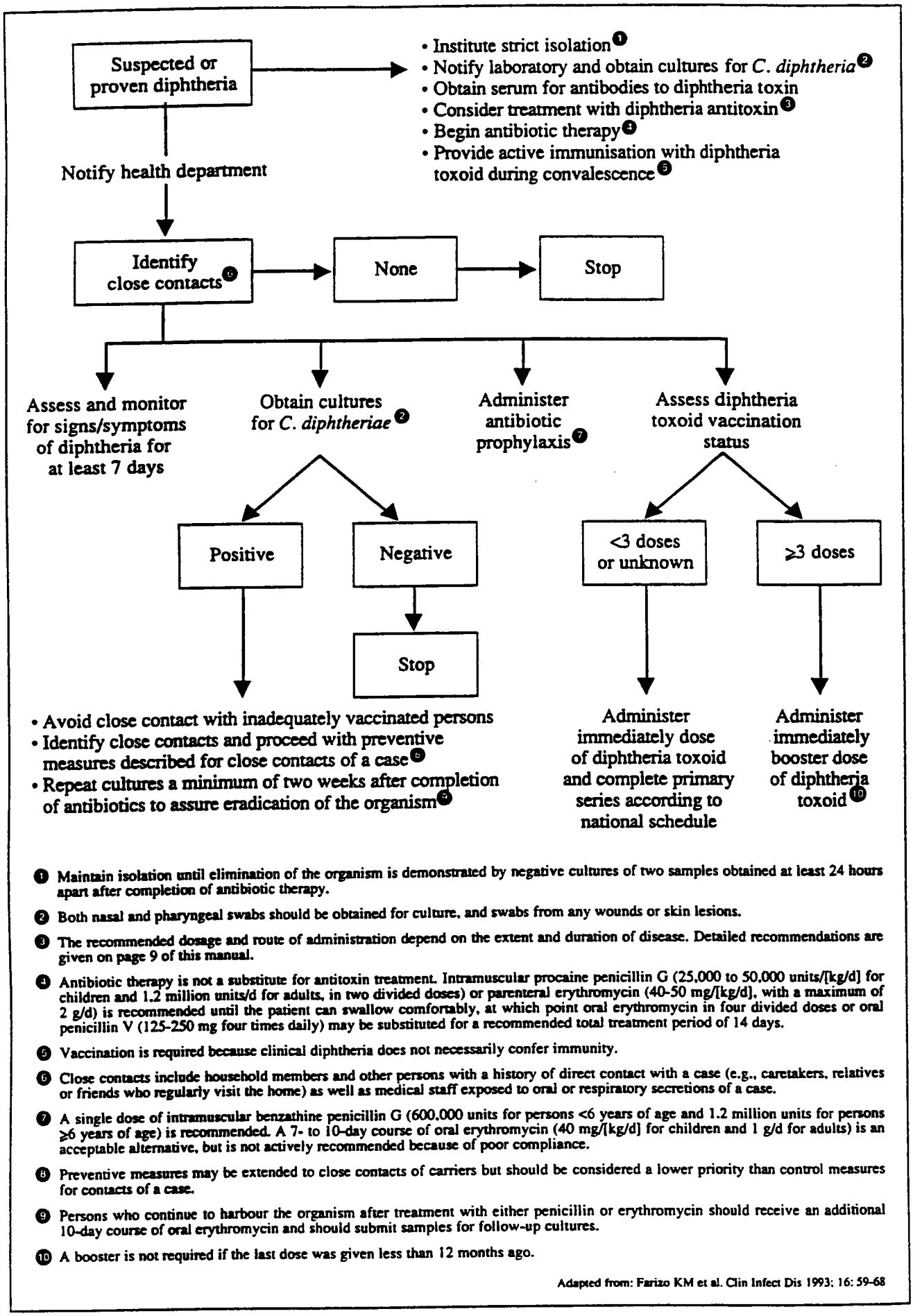
6.1 INVESTIGATION OF THE OUTBREAK

Active case finding should be implemented to ensure that no cases are missed. This could include daily telephone contact with hospitals, laboratories and schools with active follow–up of any suspicious cases, which should be investigated according to the protocol described in section 5. Cases should be classified as suspected, probable or confirmed and analysed according to age and sex, onset date and geographical distribution.

The index case(s) should be classified as indigenous or imported.

Vaccine efficacy should be estimated using the WHO screening method (Orenstein et al 1985). If efficacy is low, then further analytical studies to assess efficacy should be planned eg case–control or cohort studies, and the cause of low efficacy established (use of subpotent vaccine, inadequate cold chain etc).

The need for a serological survey should also be considered.



❶ Maintain isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antibiotic therapy.

❷ Both nasal and pharyngeal swabs should be obtained for culture, and swabs from any wounds or skin lesions.

❸ The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations are given on page 9 of this manual.

❹ Antibiotic therapy is not a substitute for antitoxin treatment. Intramuscular procaine penicillin G (25,000 to 50,000 units/[kg/d] for children and 1.2 million units/d for adults, in two divided doses) or parenteral erythromycin (40-50 mg/[kg/d], with a maximum of 2 g/d) is recommended until the patient can swallow comfortably, at which point oral erythromycin in four divided doses or oral penicillin V (125-250 mg four times daily) may be substituted for a recommended total treatment period of 14 days.

❺ Vaccination is required because clinical diphtheria does not necessarily confer immunity.

❻ Close contacts include household members and other persons with a history of direct contact with a case (e.g., caretakers, relatives or friends who regularly visit the home) as well as medical staff exposed to oral or respiratory secretions of a case.

❼ A single dose of intramuscular benzathine penicillin G (600,000 units for persons <6 years of age and 1.2 million units for persons ≥6 years of age) is recommended. A 7- to 10-day course of oral erythromycin (40 mg/[kg/d] for children and 1 g/d for adults) is an acceptable alternative, but is not actively recommended because of poor compliance.

❽ Preventive measures may be extended to close contacts of carriers but should be considered a lower priority than control measures for contacts of a case.

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

❿ A booster is not required if the last dose was given less than 12 months ago.

Adapted from: Farizo KM et al. Clin Infect Dis 1993; 16: 59-68

Figure 2. Diphtheria: recommendations for case management and investigation of close contacts

6.2 CONTROL MEASURES

The basic principles of diphtheria outbreak control are:

- achievement of high vaccine coverage in the population affected
- prompt recognition and management of diphtheria cases
- rapid invesigation and management of close contacts of cases

6.2.1 Achievement of high coverage in the population affected

The targets proposed by the WHO expert group in 1992 (section 3.2.1) should be adopted from the outset:

- every district should achieve 95% coverage with the primary immunization series (DPT3) by 2 years of age
- every district should include a booster dose (booster doses) of a diphtheria toxoid–containing vaccine in children of school age and achieve 95% coverage for this dose
- additionally, mass immunization should be carried out in schools and preschool institutions to ensure that all children are well protected against diphtheria: completion of the primary immunization course in non–immunized or incompletely immunized children, and administration of a booster dose for fully immunized children if the last injection was given more than 5 years ago.

Furthermore, **mass immunization for adults** older than 25 years of age using diphtheria–toxoid–containing vaccines (preferably Td) should be carried out for persons **belonging to groups of high risk.**

High risk groups include health care workers, armed forces, public service employees with frequent public contact, teachers, homeless people and alcoholics. Special outreach programmes will be required to immunize some of these groups, for example in social care institutions.

If the epidemiological situation demands it, the whole adult population should be included in mass immunization.

Immunization days, immunization centres and mobile immunization points should be used. Immunization carried out on a house–to–house basis may be very useful in villages and small towns. The key to success is proper preparation in collaboration with local organizations and the media.

The **list of contraindications** developed by WHO (Expanded Programme on Immunization, 1988) should be adopted nationally. It is recommended that leaflets of all diphtheria toxoid–containing vaccines should be revised urgently to ensure that no unjustified contraindications are included.

6.2.2 Prompt recognition and management of diphtheria cases

Case finding should be initiated as described in section 6.1. and case management according to the protocol outlined in sections 5.1 to 5.6.

6.2.3 Rapid investigation and management of close contacts of cases

This should be conducted according to the protocol outlined in section 5.7.

7. ROUTINE IMMUNIZATION

The standard schedule should include a minimum of three doses in the first year of life with a booster in school age (5 – 14 years) children. In addition a further booster at school leaving age is desirable.

The need for booster doses is adults should be determined by serological surveys. If the immunity rate in any age, social or ethnic group is found to be low, strategies for improving the immunity rate should be implemented. Potential strategies include routine boosters at periodic intervals, mass vaccination and opportunistic immunisation (eg before travel to an endemic area or in conjunction with other vaccinations).

All vaccines used must meet WHO requirements (WHO 1990). A low–dose toxoid preparation should be used for vaccination of older (>7–10 yrs) children and adults.

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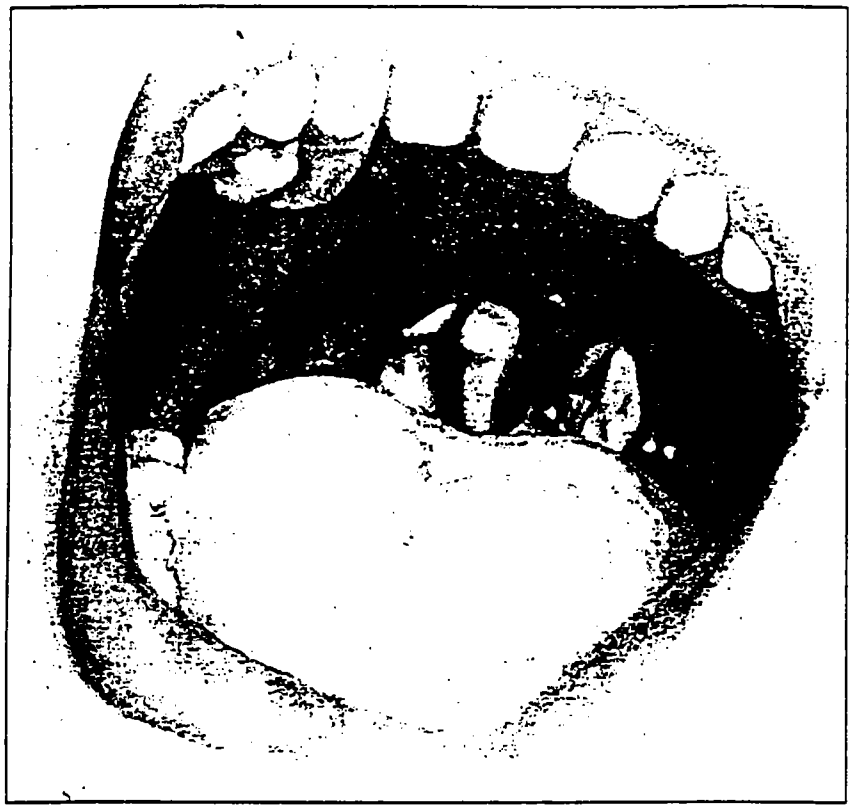

Figure 3. Typical diphtheria membrane

Characteristic clinical features of diphtheria are:

Early	• membrane • sore throat (pharyngotonsillar diphtheria) • hoarseness (laryngeal diphtheria) • stridor (laryngeal diphtheria) • blood-stained nasal discharge (nasal diphtheria) • swollen tender cervical lymph nodes
Severe cases	• swelling and oedema of the neck ("bull neck") • submucosal or skin petechial haemorrhages • toxic circulatory collapse • acute renal insufficiency
Late	• myocarditis • paralysis of soft palate • blurred vision • limb paralysis • paralysis of diaphragm