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THE CONTROL OF DIPHTHERIA IN EUROPE

Report on a WHO Meeting

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Eliminating seven specific diseases

By the year 2000, there should be no indigenous measles, poliomyelitis, neonatal tetanus, congenital rubella, diphtheria, congenital syphilis or indigenous malaria in the Region.

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THE CONTROL OF DIPHTHERIA IN EUROPE

Report on a WHO Meeting

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Note

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Introduction

During the Fourth Meeting of the European Advisory Group (EAG) of the Expanded Programme on Immunization (EPI) in Paris in February 1990, it was recommended that the Regional Office should convene an expert group to advise on vulnerability to diphtheria, especially among adults, and to develop strategies to tackle this problem.

A Meeting on the Control of Diphtheria in Europe was held, therefore, in Geneva from 17 to 19 April 1990. The aims of the Meeting were:

- to review diphtheria incidence in the European Region with respect to surveillance, reporting and the prevention of the disease by immunization in childhood and at older ages;

- to ensure that the immunization policy and schedules used by different Member States are bringing them nearer to the goals of target 5 of the regional strategy for health for all by the year 2000; and

- to draw up guidelines for sustaining high-level immunity against diphtheria in the European population.

The participants in the Meeting are listed in Annex 3. Annex 2 gives a list of national laboratories which can provide expert advice and assistance for the identification of Corynebacterium diphtheriae.

The epidemiology of diphtheria in Europe

A rapid decline in the incidence of diphtheria has been observed in almost every country in the European Region since 1961. In 1989, a total of 886 cases was reported from nine countries. Two countries (Turkey and USSR) reported 98% of these cases; a further seven countries each reported 5 cases or less. Almost a quarter of the Region's population now lives in countries free from the disease.

In countries still reporting cases, diphtheria incidence is stable or decreasing.

Over 50% of cases occur in adults. Small outbreaks in adults still occur from time to time due to gaps in population immunity.

Surveillance of diphtheria

Epidemiological surveillance

A reliable case-reporting system should exist in every country to ensure that no cases are missed. Steps should be taken to ensure that health care workers consider the diagnosis of diphtheria when any of the typical clinical features (see below) are present, irrespective of immunization status.

Cases should be classified as suspected/probable/confirmed. It was recommended that WHO set up a working group to produce a manual for field workers to help them eliminate[a] diphtheria. This manual should include criteria for classification of cases, and guidelines on the management of sporadic cases and outbreaks.

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[a] For the definition of diphtheria elimination, as opposed to eradication, see page 6.

Only confirmed cases should be reported to WHO. Sporadic cases should be reported annually. However, any outbreaks (two or more epidemiologically related confirmed cases) must be reported immediately. It was recommended that WHO adopt the following standard case definition for confirmed cases:

- either one or more typical features of diphtheria (see below), plus laboratory confirmation, i.e. isolation of a toxigenic strain of C. diphtheriae; occasionally, laboratory confirmation may be obtained by demonstrating a fourfold or greater antitoxin increase in paired sera, but only if both serum samples were obtained before the administration of diphtheria toxoid or antitoxin;

- or isolation of a toxigenic strain of C. diphtheriae from a typical cutaneous or mucosal site (skin ulcer, wound, conjunctiva, ear, vagina).

Typical features of diphtheria

(a) Local	- pseudomembrane - pharyngitis - laryngitis - tonsillitis - swollen regional lymph nodes
(b) Progressive	- stridor
(c) Malignant	- bull neck (Caesarian neck) - submucosal or skin petechial haemorrhages - toxic circulatory collapse - acute renal insufficiency - myocarditis and/or motor paralysis one to six weeks after onset.

Disease caused by C. ulcerans is excluded from this case definition.

It should also be noted that this definition differs from that used by the US Centers for Disease Control, in which illness due to non-toxigenic C. diphtheriae is included.

Laboratory surveillance

Laboratory surveillance has two aspects: first, procedures for the correct identification and characterization of C. diphtheriae strains; and second, serological surveillance of immunity.

Countries should define procedures for the routine isolation and identification of C. diphtheriae, which should include training on the proper collection of swabs and transport of specimens. It was recommended that a WHO working group be set up to produce a laboratory manual for the European Region outlining these procedures, based on the guidelines by Brooks (1). It was also recommended that a network of collaborating centres be established in Europe to improve the exchange of information about diphtheria.

Serological survey of immunity is an important tool which can be used to monitor progress towards the elimination of diphtheria. The minimum protective level of diphtheria antitoxin in a serum sample should be regarded as 0.01 IU/ml. Provided a large proportion of the population (at least 90% of children and 75% of adults) have protective antibodies, diphtheria elimination seems possible. The higher level of 0.1 IU/ml is desirable for individual protection; however, in most people it cannot easily be maintained over a long period of time. It was recommended that laboratory procedures for measuring diphtheria immunity should be adjusted to the WHO reference antitoxin preparation (2).

Serological surveys have been conducted in several European countries in recent years. These surveys have found that while immunity in children is generally high, many adults are no longer protected. This is especially true for adults over 30 whose immunity has not been boosted by natural infection. For this reason, diphtheria now occurs predominantly in adults. It is desirable for countries to conduct immunity surveys in all age groups, and formulate appropriate adult immunization strategies based on the results.

Vaccination programmes

Preparations

Details of the various vaccine preparations are contained in a previous WHO publication (3).

Schedules

The schedules for diphtheria immunization in childhood vary considerably between countries in Europe. It is not possible to be prescriptive about these schedules, as the vaccine preparations and delivery systems used in the Region are not identical.

Many countries recommend booster doses for adults. There are several strategies which can be used to achieve high levels of immunity in adults. These include routine revaccination at 10-yearly or greater intervals, mass vaccination campaigns and opportunistic immunization (e.g. before travel to an endemic area or in conjunction with other vaccinations). Where regular boosters for adults are given, attention should be paid to the possibility of adverse reactions. The use of a low-dose toxoid preparation should be considered in these circumstances.

Coverage

The most important aspect of the diphtheria elimination effort, is the achievement of high primary immunization coverage in children. Coverage with three doses should be greater than 90% by two years of age, and this coverage level should be sustained. It was recommended that a standard method of measuring childhood immunization coverage be adopted throughout the Region, as follows:

$$\text{coverage } \% = \frac{\text{number of children receiving three doses by two years of age}}{\text{target population}} \times 100$$

Elimination of diphtheria in Europe

The elimination of diphtheria means the absence of indigenous disease caused by toxigenic C. diphtheriae strains. This can be accomplished provided high immunization coverage is achieved in children and immunity is sustained in adults.

Eradication (removal of the causal agent) is not considered possible at present, because there is no evidence that vaccination with diphtheria toxoid can completely eliminate the carrier state. The target for the European Region is therefore the elimination of indigenous diphtheria by the year 2000. This is defined as absence of any confirmed indigenous cases, in the presence of a reliable reporting system. Guidelines for EPI programme managers concerning diphtheria elimination were drawn up at the Meeting (see Annex 1).

Research and development

Regarding further research and development in the diphtheria field, it was suggested that the following should in future be given high priority:

- studies on possible means of protection against the *C. diphtheriae* carrier state;

- the development of rapid, reliable laboratory methods for diagnosis of the disease, surveillance of carriers, determination of immune status and epidemiological investigation of outbreaks;

- further studies on the importance of virulence factors other than toxigenicity of the causative agent.

Summary of recommendations

1. A WHO working group should be set up to produce two manuals for field workers to help eliminate diphtheria. One manual would deal with epidemiological surveillance and control of diphtheria; the other would outline procedures for the routine isolation and identification of *C. diphtheriae*.

2. WHO should adopt a standard case definition for confirmed diphtheria cases, as outlined in this report (page 3).

3. Laboratory procedures for measuring diphtheria immunity should be adjusted to the WHO reference antitoxin preparation.

4. A network of collaborating centres should be established in Europe to improve the exchange of information about diphtheria.

5. A standard method for measuring childhood immunization coverage should be adopted throughout the WHO European Region, as follows:

$$\text{coverage } \% = \frac{\text{number of children receiving three doses by two years of age}}{\text{target population}} \times 100$$

REFERENCES

1. Brooks, R. Guidelines for the laboratory diagnosis of diphtheria. Geneva, World Health Organization, 1981 (unpublished document LAB/81.7).

2. Biological substances. International standards and reference reagents 1986. Geneva, World Health Organization, 1987.

3. International list of availability of vaccines and sera. Geneva, World Health Organization, 1989 (unpublished document BLG/1984/Rev.1).

Annex 1

GUIDELINES FOR THE ELIMINATION OF DIPHTHERIA FROM EUROPE

The target for the European Region is the elimination of indigenous diphtheria by the year 2000. This is defined as the absence of indigenous confirmed cases caused by toxigenic C. diphtheriae. Eradication (removal of the causal agent) is not considered possible at present, as there is no evidence that vaccination with diphtheria toxoid can completely eliminate the carrier state.

Achieving and sustaining immunity

Elimination of diphtheria is possible if high primary immunization coverage is achieved in young children and immunity can be sustained in adults. The minimum requirements are:

- 90% immunization coverage (three doses) before two years of age;

- maintenance of a 90% immunity rate in schoolchildren and a 75% immunity rate in adults.

Serological survey, despite its cost, is the most valuable tool in measuring population immunity. Particular attention should be paid to immunity among 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. The higher level of 0.1 IU/ml is desirable for individual protection; however, in most people it cannot easily be maintained over a long period of time.

Laboratory procedures for measuring antibodies should be adjusted to the WHO reference antitoxin preparation (1).

The strategies by which good population immunity is achieved and sustained will vary from country to country. Some countries recommend routine booster doses at 10-yearly or greater intervals. Other possibilities include mass immunization campaigns, opportunistic immunization (e.g. before travel to an endemic area or in conjunction with other vaccinations) or changing the dose and/or composition of vaccine used. All vaccines used must meet WHO requirements.[a]

Surveillance

The purpose of surveillance is to provide information on the basis of which to take appropriate preventive action.

Four major indicators may be used to monitor progress towards diphtheria elimination:

- disease incidence, reported by means of a reliable system of surveillance;
- immunization coverage in children;
- population immunity, measured by randomized serological surveys;
- toxigenic C. Diphtheriae in the population.

[a] Proposed revised requirements for diphtheria toxoid, pertussis vaccine, tetanus toxoid and combined vaccines will be published shortly in the WHO Technical Report Series (Fortieth report of the WHO Expert Committee on Biological Standardization, now in press).

All suspected diphtheria cases should be investigated and classified as non-diphtheria, probable diphtheria or confirmed diphtheria. Probable and confirmed cases should be reported to the national health authority. Guidance on the criteria to be used in classifying cases will be contained in a manual for diphtheria elimination, to be prepared by WHO. Only confirmed cases should be reported to the Regional Office for Europe of WHO. A confirmed case is defined as:

- either one or more typical features of diphtheria (see below), plus laboratory confirmation, i.e. isolation of a toxigenic strain of C. diphtheriae. Occasionally, laboratory confirmation may be obtained by demonstrating a fourfold or greater antitoxin increase in paired sera, but only if both serum samples were obtained before the administration of diphtheria toxoid or antitoxin.

- or isolation of a toxigenic strain of C. diphtheriae from a typical cutaneous or mucosal site (skin ulcer, wound, conjunctiva, ear, vagina).

Typical features of diphtheria

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- toxic circulatory collapse
- acute renal insufficiency
- myocarditis and/or motor paralysis one to six weeks after onset.

Disease caused by C. ulcerans is excluded from this case definition. It should also be noted that this definition differs from that used by the US Centers for Disease Control, in which illness due to non-toxigenic C. diphtheriae is included.

Reporting of cases to WHO should be annual; however, any outbreak (two or more epidemiologically related confirmed cases) must be reported immediately. Countries should take steps to ensure that no cases are missed. This will include increasing the awareness of health care workers of the possibility of diphtheria, and ensuring that facilities exist in all bacteriology laboratories for the routine identification of corynebacteria. Further guidance on appropriate laboratory facilities and specimen collection will be contained in the forthcoming WHO diphtheria elimination manual.

All countries should adopt a standard method for measuring immunization coverage in children, as follows:

$$\text{coverage } \% = \frac{\text{number of children receiving three doses by two years of age}}{\text{target population}} \times 100$$

Containment of sporadic cases and outbreaks

Appropriate control measures must be taken in every case. Two or more epidemiologically related cases should be considered an outbreak and reported immediately to the

national health authority and to WHO. Specific guidance on the management of cases will be contained in the WHO diphtheria elimination manual. Appropriate control measures include:

- an immediate report to the local and national health authorities;
- isolation of the case until a minimum of 24 hours' appropriate antibiotic treatment has been given;
- specific treatment of the case;
- management of contacts: consider (a) nose or throat cultures; (b) active immunization; (c) antibiotic therapy; (d) clinical surveillance.

Transmission of C. diphtheriae by inert vehicles (e.g. clothing, toys) is unlikely. It may however be necessary to perform concurrent disinfection and terminal cleaning in schools, kindergartens and patient rooms for medicolegal reasons.

REFERENCES

1. Biological substances. International standards and reference reagents 1986. Geneva, World Health Organization, 1987.

Annex 2

NATIONAL LABORATORIES WHICH CAN PROVIDE EXPERT ADVICE AND ASSISTANCE FOR THE IDENTIFICATION OF C. DIPHTHERIAE

Country	Full name and address
DENMARK	Dr I. Heron Chief, Department for Bacterial Vaccines State Serum Institute 5, Artillerivej, 2300 Copenhagen
GERMAN DEMOCRATIC REPUBLIC	Professor Waltraud Thilo Zentralinstitut für Hygiene, Mikrobiologie und Epidemiologie der DDR Wollankstrasse 15-17 1100 Berlin
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Annex 3

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