DIPHTHERIA EPIDEMIC IN EUROPE: EMERGENCY AND RESPONSE

REGIONAL OFFICE FOR EUROPE

· FOUNDATION MARCEL MÉRIEUX

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 -- prevention and control
EPIDEMIOLOGICAL METHODS
IMMIGRATION
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Report on a WHO Meeting

St Petersburg, Russia, 5–7 July 1993

Corrigendum

Page 5, para. 2, line 2

Please replace the word "vaccinated" with "unvaccinated".

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ABSTRACT

In view of the urgent need for action to combat the diphtheria epidemic in the Russian Federation and Ukraine and its spread to other countries, the Fondation Mérieux, a WHO collaborating centre, and the WHO Regional Office for Europe convened a meeting on the topic in St Petersburg in July 1993.

When routine childhood vaccination against diphtheria was introduced in the 1940s, most people older than 10 years of age were already immune from earlier infections. In countries with long-standing immunization programmes against diphtheria, a large proportion of adults are now susceptible, however, owing to: waning immunity from childhood vaccinations, the deaths of elderly people with natural immunity, little circulating diphtheria to boost immunity, and the lack of or poor compliance with adult booster policies.

The lack of diphtheria in such countries to date has probably been due to a fortuitous selective advantage against toxigenic diphtheria in the vaccinated population, leading to the disappearance of toxigenic strains. Once toxigenic strains are reintroduced in sufficient numbers to re-establish foci of infection, however, control may be difficult because of asymptomatic carriage even by immunes, respiratory spread, complicated in the current situation by political and economic changes that have reduced vaccine supply while increasing population movement.

This meeting provided an excellent first opportunity for group discussion by the key scientists, physicians, and policy-makers responsible for controlling this epidemic in Europe. Current practices and the situation in epidemic areas were described. Progress was made in the laboratory in identifying a predominant outbreak clone. Three studies showed generally reassuring vaccine efficacy results, suggesting that vaccine potency, the cold chain, vaccine administration and the accuracy of vaccination history were generally adequate, and control efforts may now focus on other areas. The participants at the meeting identified several research needs and recommended the use of well known measures to control the epidemic: the achievement of high immunization coverage in target age groups, prompt recognition and management of diphtheria cases, and rapid investigation and effective management of close contacts to prevent secondary cases. In addition, they recognized that much challenging work remains ahead before diphtheria is brought under control in Europe again.

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INTRODUCTION

Since 1990, a major resurgence of diphtheria has been observed in the WHO European Region, centred mostly in the Russian Federation and Ukraine. In view of the urgent need for action, the Fondation Mérieux, the WHO collaborating centre for health manpower development, and the WHO Regional Office for Europe convened a meeting on the diphtheria epidemic in Europe in St Petersburg from 5 to 7 July 1993:

- to review the situation in the countries affected
- to review the surveillance system
- to analyse the quality and efficacy of vaccines
- to review the case management of diphtheria patients
- to recommend an appropriate epidemic control strategy.

The meeting was attended by participants and observers from 25 countries. Dr A. Galazka served as the Chairperson and Dr R. Chen, Dr B. Bytchenko and Dr N. Chaika served as the Rapporteurs. Dr C. Roure and Dr G. Oblapenko served as Secretaries. The lists of working papers and participants comprise Annexes 1 and 2, respectively.

SITUATION ANALYSIS

The European Region

Widespread immunization with diphtheria toxoids since the 1940s had resulted in virtual elimination of diphtheria in many European countries in the 1970s. A low of 623 reported cases was reached in 1980. The proportion of countries reporting zero incidence continued to increase during the 1980s, reaching a high of 81% in 1990. Two waves of resurgence have occurred, however, one during 1982–1985 (with a peak of 1917 cases in 1983) involving several countries, and the current epidemic beginning in 1990 and affecting mostly the Russian Federation and Ukraine. Over 5000 cases were

reported in 1992 and the total for 1993 may be twice as high. The danger of the spread of the current epidemic is high. Norway and Belarus reported imported cases in 1992; in 1993, Belarus, Estonia, Finland and Poland reported imported cases from Belarus, the Russian Federation or Ukraine. The danger of the further spread of the diphtheria epidemic in other newly independent states (NIS) of the former USSR where local transmission is occurring is high because of:

- suboptimal routine immunization and other public health services in many of the new countries
- the large population of susceptible adults in most countries
- the large circulation by refugees, entrepreneurs and tourists, and
- the lack of experience with diagnosis and treatment of diphtheria by most health workers.

In 1991–1992, only 29 of the countries of the Region achieved an immunization coverage level of 90% or more with the third dose of diphtheria-tetanus-pertussis (DTP) or diphtheria-tetanus (DT) vaccine. Only 78% of the geopolitical units within countries (districts/provinces) had DTP3 or DT3 coverage of 80% or more. The WHO Regional Office for Europe has been severely challenged by the rapidly evolving political and economic situation in the Region. Since 1991, the number of Member States has increased from about 30 to about 50. Change has severely damaged vaccine supply and immunization services in many countries. The Regional Office is seeking financial assistance to help remedy these shortages.

In February 1993, the European Advisory Group (EAG) on the WHO Expanded Programme on Immunization (EPI) identified its highest priority for 1993–1995: emergency action to coordinate international and national efforts to control the diphtheria epidemic currently affecting some Member States. The EAG further endorsed a target for health for all that calls for the elimination of indigenous cases of diphtheria by the year 2000. To help attain this target, a number of operational targets were set and were reaffirmed during

the fifth meeting of the national immunization programme managers of EPI in June 1993:

> By 1995, every country should achieve 95% coverage with primary immunization by 2 years of age.
>
> By 1997, no district in any country should have less than 90% coverage with primary immunization at 2 years of age.
>
> By 1995, every country should include a booster dose of a diphtheria-containing vaccine in children of school age (5-14 years) and achieve either 95% coverage or 90% immunity based on appropriate serological studies.
>
> By 1995, all reported cases should be classified as indigenous or imported.
>
> By 1995, the diphtheria immunity status of the adult population should be assessed in all countries by appropriate serologic studies and boosters given as necessary.
>
> The occurrence of a single case of diphtheria requires immediate control measures, such as isolation of the patient, and vaccination and chemoprophylaxis of contacts. During an outbreak, special measures must be taken, including mass immunization.

The Russian Federation, Moscow and St Petersburg

The epidemiological situation in the Russian Federation was recently summarized *(1,2)*. The epidemic has spread to all areas of the country and the number of cases is still rising. In 1992, 3897 cases and 127 (3.2%) deaths were reported (double the figures for 1991). The highest incidence rates are observed in regions with highest population density; Moscow, St Petersburg and Leningrad *oblast* account for 48% of total cases. In Moscow, 49 outbreaks (including 4 large outbreaks in 3 institutions) occurred in 1992 in contrast to 7 outbreaks in 1989. The estimated economic cost of the

outbreak was over 5 million roubles. In St Petersburg, 10% of cases were found in clusters (a psychiatric hospital, preschools and large families).

Ukraine, Belarus, Estonia, Kazakhstan

The incidence of diphtheria in Ukraine has increased fifteenfold during the last three years and continues to increase; 1096 cases (with 30 deaths) were reported during the first five months of 1993, in contrast to 1101 cases in the whole of 1992. Cases were reported from all *oblasts*, although incidence is highest in urban areas such as Kiev, Odessa and Lvov. After the previous near elimination of diphtheria cases and/or toxigenic organisms, increases in diphtheria were also observed in Belarus (151 cases), Estonia (19 cases, of which 3 were fatal and 8 had established links to the Russian Federation) and Kazakhstan (91 cases) in 1990. All are experiencing difficulty in assuring adequate supply of DPT vaccine.

Adjacent countries

Finland experienced its first diphtheria case in 30 years in April 1993, when a 43-year-old male fell ill upon return from St Petersburg. Cultures for diphtheria were made of 67 close contacts: all had negative results. The diagnosis was delayed for several days, however. The surveillance for bacteriologically confirmed cases in Finland is probably adequate, but less so for mild cases or carriers.

After two decades of sporadic single cases, Poland has experienced 5 cases since 1992: 1 in 1992 and 4 in 1993 *(3)*. All cases occurred in men aged 22–26 years who had received 5–6 diphtheria vaccinations (last vaccinated at age 14) and had contacts with Belarus or Ukraine. Bulgaria, Romania and Germany report no imported cases linked to the epidemic to date.

Common patterns observed

Many common patterns have been observed in epidemic areas. The first is **evidence of adult susceptibility**. Most of the cases are among adults: 2824 of 3897 (73%) in the Russian Federation in

1992, 1202 of 1567 (77%) in Ukraine in 1992, 41 of 66 (62%) in Belarus in 1992 and 55 of 91 (60%) in Kazakhstan from 1990 to May 1992. In addition, serosurveys show increasing susceptibility with age. In the Russian Federation and Ukraine, the age group with the lowest level of diphtheria antibodies comprises people aged 20–40 years. Elsewhere, the most sensitive groups include those aged 40–50 in Poland and those over 50 years in Finland.

The second common pattern is **more severe disease and higher mortality in vaccinated people**. In Moscow 50% of severe cases were found in the unvaccinated and 1% in the vaccinated. The corresponding figures in Belarus were 32% and 7%. All deaths in Moscow and St Petersburg were among the unvaccinated.

Third, **the diagnosis of diphtheria is frequently missed or delayed**. For example, medical care was sought for 64% of unimmunized child cases during the first two days of illness but only 35% were hospitalized, and 58% of adults with severe illness were hospitalized with a diagnosis of either sore throat or peritonsillar abscess. Misdiagnosis correlated with poor outcome: 10 of 15 patients with hypertoxic diphtheria in Moscow were initially misdiagnosed.

The interval between the onset of illness and the diagnosis of diphtheria was: 0–2 days for 40% of total cases, 3–4 days for 21%, 5–6 days for 21% and 7 days or more for 15%. In Belarus, 96% of patients with tonsillitis in urban areas were cultured for *Corynebacterium diphtheriae*; the figure for rural patients was 60–70%. In Kazakhstan, only 20–30% of cases were accurately diagnosed initially; others were diagnosed only after bacteriological results or classic complications, or at autopsy.

Fourth, **many diphtheria patients had previously been vaccinated** (70% of cases in St Petersburg and 33% of child and 72% of adult cases in Belarus) thereby raising questions about vaccine efficacy. It should be noted, however, that when coverage is high and vaccine efficacy is high but not 100%, one would expect most cases to be found in vaccinated people. For example, if coverage is 100% and efficacy is 90%, 10% of the vaccinated are still unprotected; in an outbreak, 100% of the cases will have been vaccinated *(4)*.

The fifth pattern is evidence of the role of a high contact rate in the spread of the disease. Incidence is highest in areas of high population density; in 1992, for example, there were 13 cases per 100 000 in Kiev city and 3 per 100 000 in Ukraine as a whole. In Kazakhstan, 73–80% of cases were found in urban areas. In St Petersburg, 60% of adult cases are in women, probably due to contact with children. In Ukraine, incidence is highest in people aged 18–29 years although the immunity in this age group is higher than that of older people; this is probably due to a higher activity rate and contact with children in younger people.

Incidence was lowest in Ukraine in summer (1991, 1992). In St Petersburg, the great (sevenfold) increase in morbidity was noted among good handlers and public transport employees. High incidence was also noted in medical staff.

Finally, there was an **increase in the proportion of biotype *Gravis*** from 30% of cases in 1986 to 90% in 1990–1992 in St Petersburg; it accounted for 82% of cases in Ukraine.

SURVEILLANCE

Epidemiological surveillance

Epidemiological surveillance provides the information necessary to take action. For surveillance to be specific, standard case definitions need to be used. The WHO Regional Office for Europe has proposed such a case definition for diphtheria:

Suspected case	Laryngitis *or* nasopharyngitis *or* tonsillitis *Plus* pseudomembrane
Probable case	Meets criteria for suspected case *Plus* one of following: – recent (<2 weeks) contact with confirmed case – current diphtheria epidemic – stridor – bullneck

- submucosal or petechial haemorrhages
- toxic circulatory collapse
- acute renal insufficiency
- myocarditis and/or motor paralysis 1–6 weeks after onset
- death

Confirmed case — One or more typical clinical features
Plus laboratory confirmation:
- isolation of a toxigenic strain of *C. diphtheriae* from a clinical specimen; or
- fourfold or greater rise in serum antitoxin, but *only* if both serum samples were obtained before administration of diphtheria toxoid or antitoxin.

Several measures complement each other in surveillance for diphtheria. **Disease incidence** provides the ultimate measure of the outcome of the vaccination programme. **Vaccination coverage** is an indicator that measures the programme's progress, the denominator being the target age group and the numerator being the number of targeted people fully immunized. **Population immunity** is another outcome measure. Antibody titres of at least >0.1 IU/ml are needed for individual protection. The latter is more assured when antitoxin titre is >0.1 IU/ml. Serological assays should be standardized, using WHO standards and reference preparations. It is believed immunity levels of over 90% in children and over 75% in adults must be maintained for control diphtheria. Because serosurveys are expensive to conduct and the results do not change rapidly, they should not in general be used as a routine monitoring tool. Finally, the number of **circulating toxigenic strains of *C. diphtheriae*** provides another outcome measure, as they are reduced in a successful vaccination programme *(5)*.

Table 1 shows vaccination coverage data that were presented at the meeting.

High coverage in the Russian Federation and Ukraine by age 5 were confirmed in vaccine efficacy case-control studies.

Table 1 Coverage data

Country	Age	Coverage (%)					
		1987	1988	1989	1990	1991	1992
Russian Federation	by 1 (adults)	80	70	83	69	68	73 (16–60)
Moscow	by 1			39			45
	(teenagers)				99	99	98
Belarus	by 1						90
	(adults)						70
Kazakhstan	by 1						87
Ukraine	by 1						64
Ukraine	by 2						92
Ukraine	by 3						90
Finland	1–4	>95	>95	>95	>95	>95	>95
Estonia	0–14	>90	>90	>90	>90	>90	>90
Poland	0–14	>90	>90	>90	>90	>90	>90
Bulgaria	0–14	>99	>99	>99	>99	>99	>99

Laboratory surveillance

Bacteriological characteristics such as micro- and macroscopic morphology, biotype, antimicrobial susceptibility, and toxigenicity are important in the identification of *C. diphtheriae* but are of limited use in identifying individual strains. In addition, traditional methodology requires several days of testing; laboratory scientists are therefore investigating more rapid techniques for diagnosis (such as api-Coryne and the polymerase chain reaction (PCR)) and for additional discrimination among *C. diphtheriae* isolates.

Several molecular approaches were used to subtype and identify epidemic strain markers of the organism. Ribotyping, multilocus enzyme electrophoresis (MEE), and a universal primer PCR were discriminating within biotypes and (non)toxigenic isolates, and all three methods identified a predominant subtype or clone of *C. diphtheriae* among Russian isolates from 1992–1993.

MEE indicated that the clone first appeared in 1990, and preliminary ribotyping indicated that it may have spread across borders into Finland and Estonia. The PCR assay is not only promising on the basis of discrimination, but is also a more rapid and less complex subtyping system. All three methods are potentially useful for epidemic investigations but are only available in some laboratories.

CONTROL MEASURES

Health authorities were reported to have taken a variety of steps to control the epidemic:

- increasing the proportion of children fully vaccinated in the Russian Federation and Ukraine;
- revaccinating adults in the Russian Federation and Ukraine, with 2 million adults in Moscow vaccinated since 1987;
- creating a special training centre at the First Infectious Disease Hospital in Moscow to improve diagnosis and treatment of diphtheria, and attitudes towards vaccination: with 300 physicians trained in five-day workshops, a total of about 6000 medical professionals (paediatricians, internists, infectious disease specialists) attending other lectures on diphtheria in 1993; and
- creating special hospital units to improve care and reduce lethality in Moscow and Kiev.

Authorities in Ukraine have divided the country into five zones based on diphtheria incidence per 100 000 population: <1, 1–2, 3–5, 6–10 and >10. About a third of the population resides in the two zones with the lowest incidence; the immediate goal here is to keep incidence at the current low levels through the early detection and treatment of cases and carriers, and the revaccination of adults, prioritized by risk group. An estimated 15 million doses have been administered since 1990.

In Finland, an estimated 1.3–1.6 million adults (of 5 million total population) have received either Td or d vaccines since 1989. Details of the case, plus recommendations for case management,

have been published and distributed. Travellers to countries with diphtheria are recommended to receive a booster if over 10 years have elapsed since their last booster. Poland is adding a dose of Td at age 19 years to the routine vaccination schedule. Td is also being offered to workers at border check-points and travellers to countries with diphtheria. A campaign with Td targeted at people aged 20–29 years in eastern Poland is planned. Bulgaria has developed a national plan to prevent diphtheria focused on improving epidemiological and laboratory surveillance, sustaining immunity (especially in immigrants) and aggressive outbreak control.

Contraindications to vaccination

Discussion at the meeting revealed substantial differences in both thinking and practice about contraindications to vaccination between the NIS and WHO recommendations; the latter are followed by most other countries. The long list of contraindications observed in the NIS, based on certain assumptions about extreme vulnerability of infants to vaccinations, has contributed to delays in age-appropriate immunization *(1)*. This issue urgently requires resolution, especially among Russian paediatricians.

In 1990, Moscow formed special paediatric immunological outpatient clinics; in 1992 these were converted to consultation centres on vaccination for children with "contraindications". About 2000 children have since received consultations at the centres and 8000 at other institutions; all were subsequently vaccinated. These measures helped to increase the percentage of children vaccinated by 1 year of age from 31% in 1989 to 45% in 1992.

Mass immunization

In February 1993, the Principal State Sanitary Physician of the Russian Federation issued a special decree on mass immunization of the population. Immunization coverage in adults in general is now 12–69%, and 13–84% in "risk groups", (defined as vendors, transport employees, food handlers, medical and nursing staff, teachers and preschool staff). In many territories, monthly surveys are made of immunization coverage of adults.

Since the mass immunization of adults began in Moscow in 1987, about 2 million people have been vaccinated. Unfortunately, only 52–66% of the people in risk groups have been vaccinated: 68% of vendors, 66% of food handlers, 62% of teachers and 55% of medical staff.

Community involvement

The following measures have been undertaken in Moscow. A committee for diphtheria prevention has been formed, consisting of doctors, representatives of the police and military, and scientists. The mass media give weekly updates on infectious diseases and air a monthly TV and radio programme. In addition, a special video on diphtheria for the "Medicine for You" programme has been aired several times and several articles on diphtheria have been published in Moscow and Russian newspapers. All high school graduates receive individual vaccination certificates.

In St Petersburg, the following steps have been taken since January 1993. Five seminars have been conducted for staff from polyclinics, and about 1000 calls daily have been handled on an information hotline. Sixteen articles have been published in local newspapers; 1000 educational posters have been printed and distributed to polyclinics; 2 million "diphtheria is dangerous for life" posters have been printed and distributed to all homes, and 24 radio or television presentations about diphtheria have been aired. In a survey to evaluate attitudes towards vaccinations, 72 health care workers and 508 members of the public responded. Of the health care workers, 64% had been vaccinated and most (79%) had a positive attitude towards vaccination; the rest took a negative attitude (14%) or were indifferent. The reasons for refusing vaccination included age (7%), medical reasons (10%), and fear of AIDS (17%), an adverse reaction (18%) or ineffective vaccination (14%). Of the members of the public, only 34% had been vaccinated; 19% were not informed about the need, and 21% lacked the time for vaccination.

There was consensus at the meeting on the need for health authorities to respond immediately to negative articles on vaccinations in the media. On the issue of whether compulsory

vaccination is a violation of human rights, it was noted that the Helsinki Agreement has two parts, one on individual rights and one on social rights. The laws on control of infectious disease in almost all countries make it clear that individuals do not have the right to infect other people, and that this is an arena, like pollution, where the rights of society outweigh those of the individual. On the other hand, society has a duty to compensate people injured due to vaccination.

VACCINES

Quality

The diphtheria toxoid content in current diphtheria vaccine is strictly controlled by animal and *in vitro* tests, according to WHO requirements for diphtheria toxoid. Antigenicity is checked in each lot, as well as sterility and presence of blood group substances. Multiple antigen preparations in combined vaccines are accepted for licence after verification of the antigenic value of the different components, such as diphtheria and tetanus toxoids and pertussis vaccine.

Diphtheria vaccines exist in paediatric (7–25 Lf) and adult presentations (one tenth of the paediatric concentration) to avoid the allergic reactions (T-cell-mediated, IgE or Arthus' reactions) occasionally encountered from booster doses. These reactions are believed to be linked with residual protein content after purification. The frequency of more pronounced reactions is dose dependent and rare *(6)*. The production of AKDS-m has been stopped, however, following the recommendations of a WHO mission.

Immunogenicity

Immunogenicity refers to the ability of a vaccine to induce a measurable immune response in an individual. In practice, this is usually measured as the level of one or more antibodies induced by vaccination, and is assessed by serological testing. Immunity as

measured by antibody levels correlates with protection for many, but not all vaccines.

Several published studies have analysed antitoxin levels after receipt of varying doses of diphtheria toxoid. Diphtheria toxoid induces levels of antitoxin greater than 0.01 IU/ml in 88–100% of recipients after 2 doses, and 100% of recipients after 3 doses *(7)*. Levels of antitoxin fall with time after primary vaccination *(8)*, and boosters are necessary to maintain protective levels. No level of antitoxin provides complete protection against diphtheria in everyone *(9)*, however, so immunogenicity studies cannot be relied upon to determine the efficacy of diphtheria toxoid in preventing clinical disease.

In Moscow in 1990–1992, 14 000 serum samples from vaccinated children and 2000 samples from vaccinated adults were tested; 4–30% of children and 41% of adults were considered inadequately protected. In St Petersburg, 42% of adults were vaccinated but the levels of immunity in the population did not change in 1987–1992. In Ukraine, only 40–55% of adults have protective titres after one booster dose. While results from more formal immunogenicity studies of diphtheria toxoid used in the former USSR were not presented at the meeting, these results suggest that either a more potent dose or a second booster dose may be needed in adults.

Efficacy

Vaccine efficacy is defined as the degree to which diphtheria toxoid protects against disease. It is calculated by the equation:

$$\frac{\text{Attack Rate unvaccinated} - \text{Attack Rate vaccinated}}{\text{Attack Rate unvaccinated}}$$

A number of study designs are available to evaluate efficacy *(4)*. Three estimates of diphtheria vaccine effectiveness in this outbreak are available.

First, based on routine surveillance data in Moscow, the incidence rate in 1991 among unvaccinated children was estimated to be 33 per 100 000, in contrast to 5.3 per 100 000 in vaccinated

children (definition of vaccinated not given), yielding an estimated effectiveness of 84% *(2)*.

A case-control study *(4)* was conducted in Ukraine using all cases in children (under 15 years of age) reported between January and October 1992. For each case, two controls were selected at random, matched to the case by year of birth and polyclinic. The date of birth, dates of vaccination and the type of diphtheria-toxoid-containing vaccine received were abstracted from clinic vaccination cards. The vaccination status of the cases and controls was compared for the date two weeks before disease onset in the case. In the analysis, with matching at the polyclinic level, estimates of efficacy were very imprecise. Precision was increased by relaxing the matching to the *oblast* level. Results for efficacy, irrespective of type of diphtheria-toxoid-containing vaccine (AKDS, ADS, AKDS-m, ADS-m) received are shown in Table 2.

Table 2 Vaccine efficacy in a case-control study in Ukraine

Doses received	Odds ratio	Efficacy (%)	95% confidence interval
1	1.8	45.2	(-69.3, 82.3)
2	2.2	53.7	(-31.8, 83.7)
3	5.6	82.1	(62.5, 91.5)
4	12.8	92.2	(83.5, 96.3)
≥5	20.0	95.0	(88.9, 97.8)

Another case-control study was done in Moscow with the following modifications. All child cases reported from within Moscow during 1991 and 1992 were enrolled. Each case was matched to 10 controls by age, within 1 month of the birth date, and by polyclinic or district. Vaccination records were transcribed in a similar manner to the Ukraine study. Table 3 shows the results for efficacy (with the 95% confidence interval in parentheses) of any diphtheria-toxoid-containing vaccine, stratified by doses received and age of case.

Table 3 Vaccine efficacy in a case-control study in Moscow

Doses received	Efficacy (%) by age group			
	0–3	4–6	7–14	All (0–14)
≥3	98.1 (89.7, 99.7)	98.1 (94.2, 99.4)	89.4 (76.9, 95.1)	95.5 (92.1, 97.4)
≥4	100	99 (99.3, 99.7)	92.3 83.0, 96.6)	97.2 (94.8, 98.5)
≥5			95.9 (89.6, 98.4)	98.4 (96.5, 99.3)

Despite some methodological limitations in these studies, the clinical efficacy of diphtheria toxoid used in Moscow and the Ukraine appears to be high. The estimates are within the range of previously published studies. These results have three important implications.

First, children vaccinated according to the current immunization schedule can be considered to be adequately protected.

Second, priority in use of vaccines remaining after the implementation of the routine childhood vaccination programme should therefore be placed on vaccinating people who are susceptible, particularly adults.

Finally, high vaccine efficacy implies that toxoid potency at production, the cold chain, vaccine administration and the accuracy of vaccination documentation were mostly adequate. Improvements in these areas may be needed, but are not critical for diphtheria control now.

CASE MANAGEMENT

The discussion at the meeting revealed four important points in case management.

1. Alcohol abusers constituted 14% of patients with mild disease and 72% of patients with severe disease.

2. Good results were claimed for use of plasmaphaeresis in treating severe cases to prevent serious complications, such as myocarditis and neuritis.

3. Extremely large doses of antitoxin have been used for some "hypertoxic" cases: up to 1 million IU over 3–4 days.

4. A protocol for case management and investigation of close contacts was recently proposed, based on a review of the medical literature *(10)*.

RECOMMENDATIONS

In view of the alarming and continued increase of the diphtheria epidemic since 1990, the following emergency actions are recommended for countries with the epidemic in progress (the Russian Federation and Ukraine), other countries at substantial risk of importing diphtheria from this epidemic (neighbouring countries), and the WHO Regional Office for Europe. In addition, the participants recommended further research on some topics.

Countries with the epidemic

1. Health authorities should develop a coordinated plan of action for diphtheria control.

2. High levels of immunity against diphtheria should be developed and maintained in infants and young children, children of school age and adults.
   First, coverage of 95% or more with primary diphtheria immunization by 2 years of age should be achieved and

sustained. The only vaccines used should be diphtheria-tetanus-pertussis (DTP) vaccine (fulfilling WHO requirements of ≥30 IU), or in the case of true contraindications, as defined by WHO, diphtheria-tetanus (DT) vaccine, paediatric formulation.
Second, coverage of 90% or more should be achieved and sustained in children aged 5–14 years with a booster dose of diphtheria-toxoid-containing vaccine at school entry and school departure.
Third, one or two doses of diphtheria toxoid (adult formulation) should be administered to adults prioritized by risk group as determined by current epidemiological data, such as:

- residence in area with high diphtheria incidence
- membership in age group with high incidence
- membership in social or professional group with high incidence (such as health care workers, military personnel and alcohol abusers).

A sample of these vaccinated adults should be studied to determine whether an appropriate proportion (80% or more) have protective titres against diphtheria; if not, a second dose of Td should be administered to all.
Progress in achieving targeted immunity should generally be monitored by vaccine coverage. Serosurveys should only be performed periodically every five or more years.

3. The list of contraindications for immunization developed by the managers of EPI at a meeting in Budapest in 1988 should be adopted, issued, disseminated, and promoted for use by the central health authorities in each country as soon as possible. This has already been done by some of the NIS. In addition, the list of contraindications on package inserts of all diphtheria-toxoid-containing vaccines should be revised as soon as possible.

4. An extensive programme is urgently needed to reorient health workers at all levels, especially paediatricians and neuropathologists, and to educate them on the benefits and

importance of immunization, vaccine contraindications and adverse events following immunization.

5. The surveillance system should be improved in three ways. Standard case definitions should be adopted and used. Health care workers and the public should receive the training needed to ensure that diphtheria cases are diagnosed and treated as rapidly as possible. Close contacts of cases should be identified and treated according to a standard protocol. The culturing of people other than close contacts has generally yielded extremely low rates for carriage and should be discontinued.

6. An aggressive and comprehensive programme of social mobilization should be launched to combat the current misinformation or lack of information on diphtheria and diphtheria vaccination. This programme should include the dynamic and proactive use of the mass media. The key messages should be simple, short and clear. They should be developed and refined on the basis of research on the knowledge, attitudes and practices of the public towards immunization.

Countries at substantial risk

7. Countries at risk of importing diphtheria should ensure the implementation of the operational targets on diphtheria adopted by the European Advisory Group on EPI in 1993, and the measures adopted by the fifth meeting of the national programme managers of the EPI in 1993.

8. The countries should identify and rectify weaknesses in the ability of health workers and laboratories correctly to diagnose and treat diphtheria cases on a timely basis.

9. They should also ensure that travellers to countries with diphtheria are adequately immunized.

WHO Regional Office for Europe

10. The WHO Regional Office for Europe should continue to work closely with Member States, donors and other groups to assure the supply of vaccine, antitoxin, antibiotics and other necessary materials to control the epidemic.

11. Guidelines and field guides for the investigation of suspect cases should be developed and disseminated as soon as possible.

12. A working group of laboratory scientists should be formed to develop guidelines and to outline future study needs and directions for laboratories, especially for the development and implementation of more rapid diagnostic assays (including toxigenicity testing).

13. The Regional Office should provide leadership and coordination of the international and national efforts to control the diphtheria epidemic in the European Region. Close follow-up (through technical consultations and periodic expert meetings, for example) should be maintained to ensure:
    - the timely implementation of recommendations from the current and recent meetings on diphtheria control;
    - the monitoring, evaluation and modification of current control strategies on the basis of surveillance, epidemiological and other scientific data.

Research needs

14. Research should be carried out in the following areas:

    (a) surveillance issues:
        - definition of high-risk groups;
        - completeness of case finding via current surveillance;
        - alternative approaches to assessing immunization coverage;

(b) outbreak control issues:

- developing valid contraindications based on scientific studies;
- determining the knowledge, attitudes and practices of the population and health care workers towards immunization;
- determining the immunogenicity and reactogenicity of booster dose in adults (of various age groups, at various Lf and in 1 or 2 doses);
- determining the efficacy of various control strategies;

(c) laboratory issues:

- standardization of passive haemagglutination diphtheria antibody assay versus WHO reference sera;
- cost-effectiveness of making cultures for diphtheria from people who are not close contacts of patients;
- rapid diagnostic tests for *C. diphtheriae* and toxigenicity;

(d). clinical issues:

- optimal antitoxin doses versus severity;
- efficacy of plasmaphaeresis.

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Annex 1

WORKING PAPERS AND BACKGROUND DOCUMENTATION[a]

Working papers

ICP/OCD 199 g20/6	EPI in Europe in the 1990s, by C. Roure
ICP/OCD 199 g20/7	Diphtheria in Europe 1995–1992, by G. Oblapenko & A. Galazka
ICP/OCD 199 g20/8	Diphtheria epidemic in Russia, by A. Monissov & N. Vaganov
ICP/OCD 199 g20/9	Epidemic of diphtheria in Ukraine, by Dr Marevsky & A. Moiseeva
ICP/OCD 199 g20/10	Control of diphtheria epidemic in Moscow: efficacy of measures taken, by N. Filatov, G. Ghistjakova & S. Markina
ICP/OCD 199 g20/11	Diphtheria epidemiology in St Petersburg: epidemiology and control, by V. Kurchanov, O. Parkov, E. Timopheeva & F. Noskov
ICP/OCD 199 g20/12	Population immunity to diphtheria in Germany, by W. Thilo
ICP/OCD 199 g20/13	Control of diphtheria in Belarus in 1990–1992, by V. Filonov, V. Gukovsky & D. Zacharenkova
ICP/OCD 199 g20/14	Diphtheria in Kazakhstan, by A. Reimer & A. Kurmangalieva

[a] Copies can be obtained from the Communicable Diseases unit, WHO Regional Office for Europe, Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark.

ICP/OCD 199 g20/15	Mass immunization: experience, problems: in the Russian Federation, by N. Gilina, V. Sadovnikova & I. Timachakovskaia
ICP/OCD 199 g20/15a	Mass immunization: experience, problems: in Ukraine, by A. Moiseeva & R. Goida
ICP/OCD 199 g20/15b	Mass immunization: experience, problems: in St Petersburg, by M. Ocuneva & I. Vorontsov
ICP/OCD 199 g20/15c	Mass immunization: experience, problems: in Moscow, by R. Litkina & R. Leshkevith
ICP/OCD 199 g20/16	Surveillance of diphtheria: main principles, by D. Salisbury
ICP/OCD 199 g20/17	Surveillance of diphtheria in the Russian Federation, by A. Jasinsky, E. Kotova, N. Maksimova & N. Tichonova
ICP/OCD 199 g20/18	Surveillance of diphtheria in Finland, by M. Jakkola
ICP/OCD 199 g20/19	Surveillance of diphtheria in Poland, by W. Magdzik
ICP/OCD 199 g20/20	Surveillance of diphtheria in Bulgaria, by S. Popova
ICP/OCD 199 g20/21	Characterization of diphtheria strains circulation in the Russian Federation in 1990–1993, by I. Mazurova, R. Zaikin & S. Cambarova
ICP/OCD 199 g20/22	Characterization of diphtheria strains isolated in the Russian Federation and in Ukraine, by I.K. Wachsmuth
ICP/OCD 199 g20/23	Characterization of diphtheria strains circulation in Ukraine in 1990–1993, by Dr Glushkevich

ICP/OCD 199 g20/24	Characterization of *Coryne bacterium diphtheriae* from north-western Russia and surrounding countries, by A. Efstratiou et al.
ICP/OCD 199 g20/25	Characterization of *C. diphtheriae* strains: a simple, fast and standardized method, by E. Estrangin
ICP/OCD 199 g20/26	Molecular typing of *C. diphtheriae,* by P. Grimont
ICP/OCD 199 g20/27	Efforts to change the negative attitude of the public and health staff towards immunization
ICP/OCD 100 g20/27a	Efforts to change the negative attitude of the public and health staff towards immunization, by L. Colosova & V. Sadovnikova
ICP/OCD 100 g20/27b	Efforts to change the negative attitude of the public and health staff towards immunization, by V. Fisenco, E. Deduh & N. Filatov
ICP/OCD 100 g20/27c	Efforts to change the negative attitude of the public and health staff towards immunization, by A. Rachmanova & G. Kolesnikov
ICP/OCD 100 g20/27d	Efforts to change the negative attitude of the public and health staff towards immunization, by N. Goida & A. Moiseeva
ICP/OCD 199 g20/28	Control measures: community involvement in Ukraine, by A. Moiseeva
ICP/OCD 199 g20/29	Post-vaccination events, by Ozeretskovsky
ICP/OCD 199 g20/30	Vaccine efficacy: results of case-control study in Kiev and Moscow, by I. Hardy
ICP/OCD 199 g20/31	Combined vaccines with diphtheria component, by L. Teulières

ICP/OCD 199 g20/32	Clinical characterization of diphtheria patients and their management, by M.P. Korjinkova & T. Platonova
ICP/OCD 199 g20/33	Experience of the Botkin's Infectious Disease Hospital in St Petersburg in case management of diphtheria, by Y. Chernishov, V. Russaltchuk & E. Volova
ICP/OCD 199 g20/34	Clinical management of diphtheria in Ukraine, by G. Vosianova

Background documentation

EUR/ICP/EPI 018	Expanded Programme on Immunization: report of the Meeting of National Programme Managers, Budapest, 26–29 April 1988
ICP/EPI 034	Fifth Meeting of National Programme Managers on the EPI, Vienna, 2–4 June 1993

Annex 2

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