CDAlert

Monthly Newsletter of National Institute of Communicable Diseases,
Directorate General of Health Services, Government of India

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DIPHTHERIA - A RE-EMERGING THREAT

INTRODUCTION

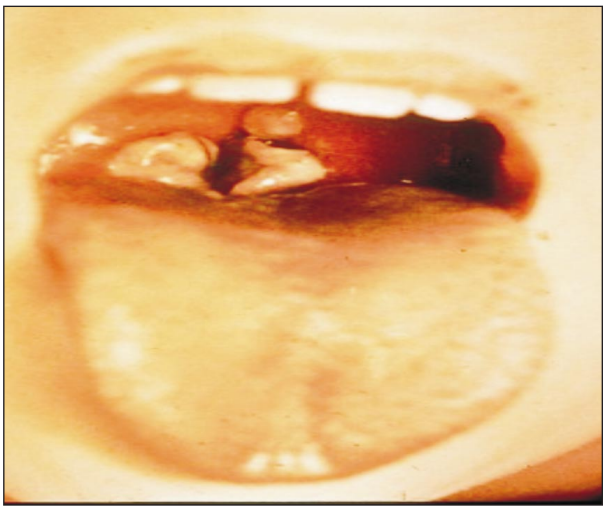
Diphtheria is an acute bacterial infection/ disease caused by Corynebacterium diphtheriae (C. diphtheriae) primarily involving tonsils, pharynx, nose, occasionally other mucous membranes or skin and rarely vagina and conjunctiva. The characteristic lesion, caused by liberation of a specific cytotoxin, is an asymetrical adherent, grayish white membrane called pseudomembrane. Some toxin producing strains of C.diphtheriae can result in systemic features like myocarditis, polyneuritis and other systemic effects. Respiratory diphtheria is usually caused by toxigenic strains, whereas cutaneous one is frequently caused by non toxigenic strains. Man is the only reservoir of the organism.

ETIOLOGY

The causative agent (C.diphtheriae) also known as Klebs Loeffler's bacillus is a gram positive, irregularly stained rod shaped, non motile bacteria producing exotoxin. The bacteria are club shaped and arranged in a Chinese letter pattern (Cuneiform arrangement). The bacteria are recognized by the presence of characteristic bluish gray metachromatic granules (Babes Ernst granules) using special staining like Albert's staining. The organism produces gray to black colonies on tellurite containing media and cream coloured colonies on Loefflers media. There are 3 biotypes of this organism gravis, intermedius and mitis; recently a fourth biotype belfanti has also been described. Generally infections caused by gravis subspecies tend to be more severe than those by mitis subspecies. In our country, all the 3 subspecies are prevalent in different proportions in different geographical locations, though, in general gravis subtypes are more commonly seen. The genes for toxin production are present in specific bacteriophages (Beta phages) and non toxigenic strains can become toxigenic by acquiring these genes through bacteriophages. Diphtheria bacilli are readily inactivated by heat and chemical agents,they may survive for a few days in dust and fomites. Other potentially toxigenic species are C.ulcerans and C. pseudotuberculosis.

CLINICAL FEATURES

After an incubation period of 2-5 days (range 1-7 days), the illness is characterized by sore throat with low grade mild fever, varying



degree of dypsnoea, pallor and sub maxillary lymphadenopathy. Usually, the tonsils exhibit grayish white, smooth fibrinous membrane that is highly adherent and extends into the pharynx, also known as pseudo membrane. The membrane could be a small patch on one tonsil to extensive involvement of both tonsils, uvula, soft palate and pharyngeal wall. The lymph nodes may become tender and enlarged. In severe cases, there is marked swelling and oedema of the neck. Laryngeal diphtheria often presents with cough and hoarseness of voice. Patients with nasal diphtheria may present with unilateral or bilateral serosanguinous discharge associated with irritation of anterior nares.

Cuatneous diphtheria, mainly seen in tropical countries, presents with morphologically distinct "punched out" ulcers covered with necrotic slough. Systemic manifestations can present with listlessness, pallor, respiratory difficulty, tachycardia and paralysis of the soft palate and ultimately leading to vascular collapse. Pneumonia occurs in more than half of fatal cases of diphtheria. Less common complications include renal failure, encephalitis and cerebral infarction. Mortality rates up to 30-40% can be seen in untreated cases, use of antitoxin reduce the case fatality to 5-10%.

PATHOGENESIS

Susceptible persons may acquire toxigenic diphtheria bacilli in the nasopharynx. The organism produces a toxin that inhibits cellular protein synthesis and is responsible for local tissue destruction and membrane formation. The toxin produced at the site of the membrane is absorbed into the bloodstream and is disseminated through lymph channels and blood to the susceptible tissues of the body. The toxin also causes low platelet counts (thrombocytopenia) and proteinuria.

CURRENT CASE DEFINITION FOR SURVEILLANCE (WHO Case definition for surveillance)

Suspected - Not applicable.

Probable case definition

The current clinical case definition of diphtheria for surveillance purposes is: "An upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsils (s), pharynx, and/or nose".

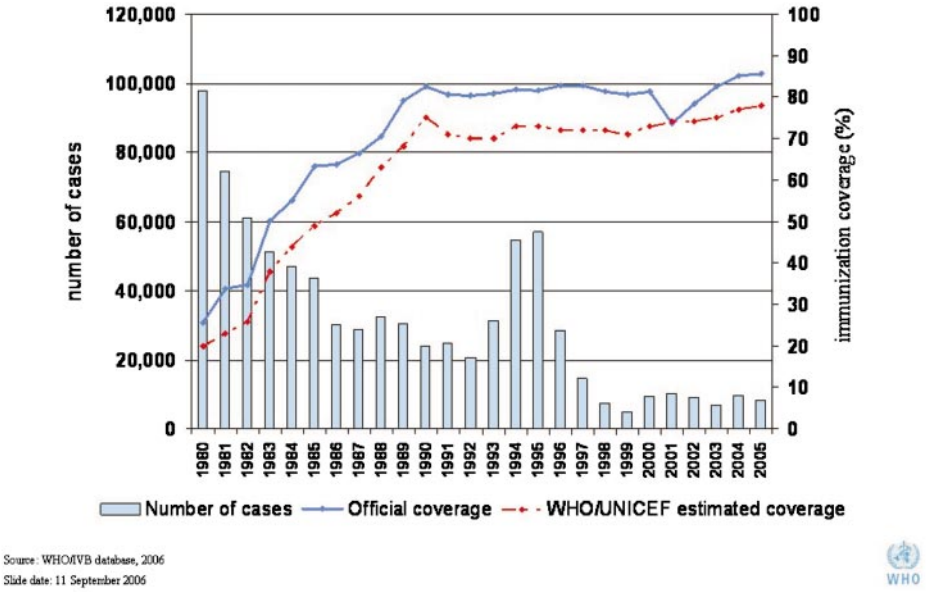
Confirmed case definition

A probable case supported by laboratory evidence either by (1) Isolation of the organism from a clinical specimen or (2) demonstration of a four-fold or greater rise in serum antibody titres in paired sera samples (only if both serum samples are obtained before the administration of diphtheria toxoid or antitoxin).

EPIDEMIOLOGY

Humans are the only reservoir of infection, transmission occurs primarily by close personal contact with a case or carrier. The infective material may comprise of nasopharyngeal secretions, discharges and skin lesions, contaminated fomites etc. Cases range from sub clinical to frank clinical cases, the former being more common source of the agent. The period of infectivity in a case may range from 14 to 28 days from the onset of symptoms. The carriers are also an important source of infection, the ratio being 95 carriers for 5 clinical cases. Carriers may be temporary (upto 1 month) or chronic (upto 1 year), nasal or throat. The nasal carriers are more important as source of infection because of the frequent shedding of the organism in the nasal secretions. Carrier rate in the community may range from 0.1 to 5%. Immunization does not prevent the carrier state, though it can be treated by the use of antibiotics.

Diphtheria global annual reported incidence and DTP3 coverage, 1980-2005



Source: WHO/IVB database, 2006
Slide date: 11 September 2006

WHO

Diphtheria mainly affects children aged between 1 to 5 years, however due to good vaccine coverage worldwide, a shift in age incidence has been observed from preschool to school age (5-15 yrs) with more and more cases being reported even in adults. Various surveys in the country based on Schick test have shown that 19-77% of adults in the country are susceptible to the disease Alcoholism, low socioeconomic status and crowded living conditions are the other risk factors for diphtheria.

Cases of diphtheria occur in all seasons, although more cases are seen during the months October to January.

DISEASE BURDEN

Global scenario

Diphtheria occurs worldwide, but clinical cases are more prevalent in temperate zones.

Due to wide spread immunization in the recent years, there has been a marked decline in the reported cases of diphtheria since eighties with nearly one lac cases reported by WHO in 1980 and only 12735 cases in 2005 out of which nearly 80% were from India.

Indian scenario

The incidence of the disease has also declined in India over the years because of wider vaccination coverage in the children below five years of age with only 2817 cases being reported

Table-1: The reported diphtheria cases in India for the last few years (CBHI data)

Year	Cases	Deaths
2007	3354	37
2006	2834	66
2005	5826	68
2004	8465	126
2003	4236	107
2002	5301	125
2001	5472	89
2000	5125	101
1999	2919	
1998	3202	143
1997	2817	162
1996	4855	296
1992	8000	
1982	17191	
1980	39231	

in year 1997, whereas in the year 1980 a total of 39,231 cases were reported (CBHI data). Thereafter, there has been sudden increase in cases with more than 8000 cases reported in the year 2004 (Table-1).

Outbreaks

The last two decades have seen a resurgence of diphtheria in both developed and developing countries where it was previously well controlled.

- An epidemic that began in **1990** in the newly independent state of the former **Soviet Union** reported more than 1,57,000 cases and 5000 deaths by the end of **1998**. Epidemic began in 1990 with 1436 cases and peaked in 1995 (50,000 cases) and waned by 1998. Most of the cases (60-77%) and fatalities occurred in adults. The proportion of cases that were microbiologically confirmed ranged from 29-95% (varying in different geographical regions). The case fatality rate ranged from 3-23%.
- In the year 2000,an outbreak of diphtheria occurred in **Cali (Columbia)** accounting for **458** suspected cases affecting subjects mainly below **20 years** of age, the case fatality being **12.5 %**
- Another outbreak of diphtheria took place in **Southern Afghanistan** in 2003, with more than 25 % of cases occurring in population older than 10 years.

Indian Scenario

- In Nov **1977**, there was a small outbreak of pharyngeal diphtheria in staff of a girl's school in Eastern Kolkatta (West Bengal). Surprisingly the age group of the affected population ranged from 20 to 63 years. Thereafter, not many outbreaks were reported in the country, though the disease have been widely prevalent in the country.
- Another small outbreak of pharyngeal diphtheria was reported in 2000 in Delhi from All India Institute of Medical Sciences, a tertiary care hospital of the country.
- During the years, **2002-03**, two small outbreaks of pharyngeal diphtheria were reported from district Baramullah (J&K) at short intervals, both were due to C.diphtheriae.

Laboratory Diagnosis

Diphtheria is no longer diagnosed easily on clinical grounds due to more and more atypical presentations, Often, the first indication of the likelihood of diphtheria is given by the laboratory. The laboratory diagnosis primarily depends on either **a) Isolation** of the organism from clinical specimens or **b) Demonstration** of a four fold rise in antibody titre in paired sera samples collected 10-14 days apart **(Both samples are to be collected before administration of either diphtheria toxoid or antitoxin)** using either **IHA** or **ELISA** test.

Note:

- Smear examination after **Gram's/Albert** staining only gives a presumptive/ suggestive diagnosis and cannot be used for purpose of reporting.
- Serological tests are not common in routine practice as the tests are not available in most of the laboratories and it is not feasible to collect paired sera samples in suspected cases of diphtheria before giving antisera.

Collection, storage and transportation of samples

A. For isolation of the organism: It is extremely important to collect appropriate samples for a quality laboratory result. In suspected cases of pharyngeal or nasal diphtheria, swabs have to be collected, in duplicate, from both the throat and nose, before antibiotic administration.

Throat swab collection: Using a sterile cotton swab, rub the inflamed part of the throat which is

red or white and located on the tonsils or fauces and collect the membrane, if present. If nothing abnormal is seen, swab the tonsils, the fauces and back of the soft palate and immediately put in the sterile tube/container and transport to the laboratory at the earliest. In case of delay of more than 48 hours, refrigerate at 2-8°C or inoculate on suitable transport medium eg **Loeffler's serum slope** or **Amie's media** and retain the swabs inside.

Similarly swabs can be collected from the skin lesions and wounds, in case of **cutaneous diphtheria** and transported similarly

B) Samples for serology: Normally, serological tests are not advised, however, in case, facilities exist for same, collect 3-5 ml of whole blood in a sterile screw capped container, the first sample collected as early as possible after onset of illness and second sample 10-14 days later before administration of antitoxin to the patient. The blood/sera after separation to be transported to the laboratory at the earliest at 2-8°C.

The samples to be subjected to the following tests in the laboratory

i. Microscopic examination of stained smears prepared from swabs

a) Gram staining - The Gram stain may show gram positive bacilli suggestive of diphtheria.

b) Albert's staining - Multiple club-shaped forms that look like Chinese characters which demonstrate the presence of metachromatic granules.

(Other Corynebacterium species (diphtheroids) that can normally inhabit the throat may give a false diagnosis).

ii. Culture

Processing of swab

Swab should be inoculated on sheep blood agar, Loefflers medium and blood tellurite agar and incubated for 24-48 hours at 37°C. On Loeffler's media, the growth can be seen sometimes as early as 6-8 hours, whereas on tellurite Blood agar, it may take 24 to 48 hours. Any suspected isolates of C.diphtheriae should be subjected to the following tests

1. Biotyping
2. Toxigenicity testing (**Elek's** test)
3. Antibiotic susceptibility test by **MIC (E test)** method

Note: All C.diphtheriae isolates should be reported including non toxigenic ones.

Drug resistance : C.diphtheriae is generally considered to be highly sensitive to antibiotics like Penicillin, Erythromycin, Cephalosporins and Quinolones. However, in the last decade, more and more cases of drug resistance to Co-trimoxazole, ampicillin, tetracycline and chloramphenicol are reported worldwide including India. There are a few reports of resistance to even penicillin and erythromycin in other countries. It is therefore imperative to carry out drug sensitivity testing in all the isolates of C.diphtheriae.

CASE MANAGEMENT

Administration of diphtheria antitoxin at the earliest is the most important element in the treatment of diphtheria, specially, respiratory diphtheria. The antitoxin should be given either by Intramuscular (I.M) or intravenous (I.V) route in doses ranging from 10,000 to 100,000 units or more depending on the severity and location of the lesion/disease after a preliminary sensitivity test either by skin or conjunctival test to determine hypersensitivity to horse serum since the antitoxin is prepared in horse sera. In addition to antitoxin, every case should be treated with appropriate antibiotics as described below.

Persons with suspected diphtheria should be placed in appropriate isolation depending on the site of infection at least for initial 48 hours after

Table-2: Dosage of antitoxin recommended for various type of diphtheria.

Type of diphtheria	Dosage (Units)	Route
Nasal	10,000-20,000	Intramuscular (IM)
Tonsillar	15,000 - 25,000	IM or intravenous (IV)
Pharyngeal or laryngeal	20,000 - 40,000	IM/IV
Combined types or delayed diagnosis	40,000 - 60,000	IV
Severe diphtheria-for example, with extensive membrane and/or severe oedema (bull-neck diphtheria)	40,000 - 100,000	IV or part IV and part IM

the provisional clinical diagnosis is made and appropriate cultures are obtained without waiting for the laboratory results. Respiratory support and airway maintenance should also be provided as needed. Dosage of antitoxin recommended for various type of diphtheria shown in Table-2.

Use of antibiotics

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

PREVENTIVE & CONTROL MEASURES

Community: The only effective way is by active immunization of all infants with diphtheria toxoid as early as possible in life as per schedule with subsequent boosters every 10 years. The aim should be to immunize before the infant loses maternally acquired antibodies so that there would be continuous protection from birth without any gap in immunity. The toxoid vaccine is available in different forms as mentioned below:-

Combined/mixed vaccines

- DPT (Diphtheria, Pertussis, Tetanus) vaccine
- DTaP (Diphtheria, acellular Pertussis, Tetanus) vaccine
- DT (Diphtheria,Teatanus toxoid) vaccine
- dT (Diphtheria, Tetanus -adult type) vaccine
- DTaP, IPV, HepB (Diphtheria, acellular Pertussis,Tetanus with hepatitis B and Polio)

Single vaccines

- FT (Formal toxoid)
- APT (Alum precipitated toxoid)
- PTAP (Purified toxoid aluminium phosphate)
- PTAH (Purified toxoid aluminum hydroxide)

(Pediatric formulations (DT, DPT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3-4 times as much diphtheria toxoid.)

National Vaccination schedule

For immunizing infants, DPT vaccine is given to children from 6 weeks upto 6 years of age. The usual schedule is a primary series of 4 doses at 2, 4, 6 months and at 16-24 months of age. The first, second and third dose should be separated by a minimum of 4 weeks. The fourth dose should follow the third dose by no less than 6 months, and should not be administered before 12 months of age. Another dose of DT should be given at 5-6 years of age. (A second dose of DT can be given month after the first dose of DT in case there is no definite history of previous immunization with DPT).

Mode of administration: All vaccines containing adjuvants should be given by deep intramuscular injection in the upper and outer quadrant of the gluteal region (In children under 1 year of age, antero lateral aspect of thigh is the preferred site for vaccination)

Storage: The vaccine should be stored at 2-8^{o}C and should never be frozen.

Adverse reactions following vaccination

Local reactions, generally erythema and induration with or without tenderness, are common after the administration of vaccines Exaggerated local (Arthus-type) reactions are occasionally reported. Rarely, severe systemic reactions such as generalized urticaria, anaphylaxis, or neurologic complications have been reported following administration of the toxoid.

Contraindications and Precautions to Vaccination

Persons with a history of a severe allergic reaction following a prior dose should not receive additional doses of toxoid.

Immunogenicity and Vaccine Efficacy

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

Suspect Case Investigation and Control measures:

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

- Immediately report to the state health authorities
- Obtain appropriate clinical samples and preliminary clinical and epidemiologic information (including vaccination history).
- Begin early presumptive treatment with antibiotics and antitoxins as described. Impose strict isolation until at least two cultures are negative 48 hours after antibiotics were discontinued.
- Identify close contacts, especially household members and other persons directly exposed to oral secretions of the patient. Carry out culture for C.diphtheriae in respiratory clinical samples of all close contacts, and assess their immunization status. Further action will vary in different situations a) In case primary immunization was received within previous 2 years, no further action is needed b) where primary course was received more than 2 years back, a booster dose of diphtheria toxoid may be given and c) Non immunized close contacts should receive prophylactic antibiotics i.e either benzathine penicillin (600,000 units for persons younger than 6 years old and 1,200,000 units for those 6 years old and older) or a 7 to 10 day course of oral erythromycin, (40 mg/kg/day for children and 1 g/day for adults).
- Treat any confirmed carrier with an adequate course of antibiotic (Erythromycin orally 40mg/Kg/day for children and 1gm/day for adults for 10 days), and repeat cultures at a minimum of 2 weeks after finishing the course of antibiotics to ensure eradication of the organism. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of erythromycin and should submit samples for follow-up cultures.

DISEASE OUTBREAKS REPORTED BY THE STATES THROUGH IDSP FOR THE MONTH OF JULY, 2008 (27th WEEK- 30th WEEK)

Sr. No	Name of State	Name of District	Disease/ Illness
1	**Andhra Pradesh**	Ananthapur	Food poisoning
		Hyderabad	Food poisoning
		Khammam	ADD
		Krishna	ADD, Food poisoning
2	**Arunachal Pradesh**	Kurung Kumey	Measles
3	**Assam**	Hailakandi	Malaria (2 outbreaks)
4	**Chandigarh**	Chandigarh	Cholera
5	**Delhi**	Delhi	Dengue
6	**Gujarat**	Kachchh	ADD
7	**Haryana**	Karnal	Measles
		Panchkula	Cholera
8	**Karnataka**	Bagalkot	Food Poisoning
		Belgaum	Food Poisoning
		Bidar	ADD
		Chamarajnagar	ADD
		Gadag	ADD
		Kolar	Dengue
		Mysore	Chikungunya
		Tumkur	Chikungunya
9	**Kerala**	Kannur	Chikungunya
		Idukki	Viral Hepatitis
10	**Madhya Pradesh**	Khargone	ADD
11	**Maharashtra**	Ahmednagar	Malaria (2 outbreaks)
		Aurangabad	Malaria

Sr. No	Name of State	Name of District	Disease/ Illness
11	**Maharashtra**	Dhule	Malaria
		Jalgaon	ADD, Dengue
		Kolhapur	ADD
		Nagpur	Viral Encephalitis, ADD
		Nashik	Malaria (3 outbreaks)
		Raigad	ADD
		Ratnagiri	ADD
12	**Nagaland**	Dimapur	AFP
13	**Orissa**	Boudh	ADD
		Ganjam	ADD
		Koraput	ADD
		Sambalpur	ADD
14	**Rajasthan**	Alwar	ADD
15	**Tamil Nadu**	Tiruchirapally	Viral hepatitis
		Villupuram	ADD
16	**Uttarakhand**	Almora	Viral hepatitis
		Pauri Garhwal	ADD
		Uttarakashi	ADD
17	**Uttar Pradesh**	Balrampur	ADD
		Lucknow	Food poisoning
		Unnao	ADD
18	**West Bengal**	Burdwan	ADD
		Hooghly	Food poisoning, ADD
		Parganas	ADD

Weekly alerts of outbrek reporting for the month of July, 2008 (27th wk. - 30th wk.)

Week No. (Date)	Total no. of States reported	No. of outbreaks reported
27 (30.6.08-6.7.08)	28	19
28 (7.7.08-13.7.08)	26	17
29 (14.7.08-20.7.08)	21	11
30 (21.7.08-27.7.08)	20	10

Total no. of outbreaks reported in the month of July, 2008

Disease/ Illness	No. of Outbreaks
Acute Diarrhoeal Disease	25
Acute Flaccid Paralysis	1
Chikungunya	3
Cholera	2
Dengue	3
Food Poisoning	7
Malaria	9
Measels	2
Viral Encephalitis	1
Viral Hepatitis	3

24X7 IDSP CALL CENTER (Toll free no. 1075)

The IDSP call center has been established to collect supplemental information on disease alert from across the country. The National Informatics Centre is maintaining the Call Centre accessible through the toll free number 1075 from all over the country by fixed and mobile phones. We encourage that all Health Care Providers utilize this day and night service to report all events of public health importance including alerts on Epidemic Prone Diseases like Cholera, Measles, Plague, Malaria, Typhoid, Dengue, Chikungunya, Leptorspirosis, Viral Hepatitis, Japanese Encephalitis, Meningococcal meningitis and AFP or any unknown syndrome in any family or workplace or locality.

...about CD*Alert*

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