

15<sup>th</sup> August 2017

## POLICY BRIEF

# DIPHTHERIA

A battle not yet won...



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Based on studies carried out in collaboration with:

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## EXECUTIVE SUMMARY

Diphtheria, caused by a toxin (poison) released by bacteria *Corynebacterium diphtheriae*, is primarily an upper respiratory tract infection.

Mortality rate, generally 5 to 10%, may be as high as 20% in children <5 yr and adults > 40 yr of age.

Treatment with Antibiotics is not enough. Administration of Diphtheria Antitoxin (DAT), an antidote (anti-poison), is required to save lives.

Incidence, which was > 1 mn /year in early 19<sup>th</sup> Century, declined >95% by 20<sup>th</sup> Century, due to active immunization. It is part of DTaP, free immunization in India.

Despite being vaccine preventable, it is reemerging in various states including Karnataka with increasing deaths.

Poor immunization coverage, lack of awareness, facilities for diagnosis and unavailability of DAT (anti-poison) are the root causes.

Increasing immunization coverage is ultimate solution but may take decades to achieve more than 90%.

## RECOMMENDATIONS

1. Ensuring availability of antidote (DAT) at least in District Hospitals & CHCs of endemic areas to prevent mortality.
2. Increasing awareness by IEC activities.

## ANTICIPATED OUTCOME

Immediate reduction in diphtheria-related mortality.

## Context

### The disease:

Diphtheria is a serious disease caused by a toxin (poison) producing bacteria *Corynebacterium diphtheriae*. It is characterized by its formation of thick grey leathery membrane in the back of the throat making voice hoarse, difficult to breathe and swallow.

IT CAN BE FATAL. The mortality rate, which is generally 5 to 10%, may be as high as 20% in children below five years and adults over 40 years of age.<sup>[1]</sup>

### Who are at risk?

Children and adults who are unimmunized or partially immunized.

### How is it transmitted?

Through (i) respiratory droplets through coughing and sneezing (ii) Toys or objects infected with the bacteria (iii) Contact with open sores (skin lesions) (iv) Infected clothing/bedding, etc.

### What is the treatment?

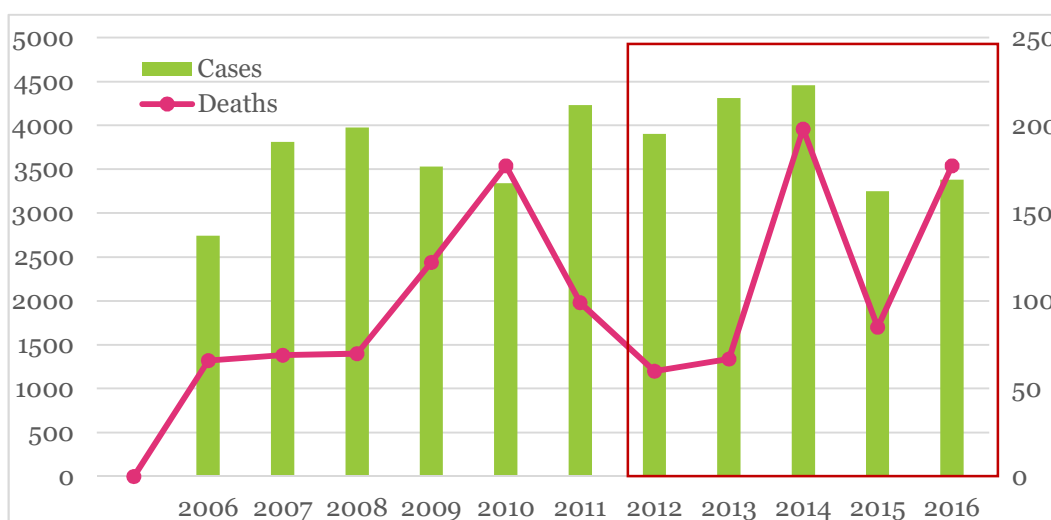
Treatment includes antibiotic therapy that kills the bacteria. But administration of DAT (Diphtheria Anti-Toxin) is required in serious cases to neutralize the toxin (poison) already released by the bacterium in the body.

### What are the complications?

Complications include (i) Difficulty in breathing (ii) Heart failure (iii) Paralysis and (iv) Death.

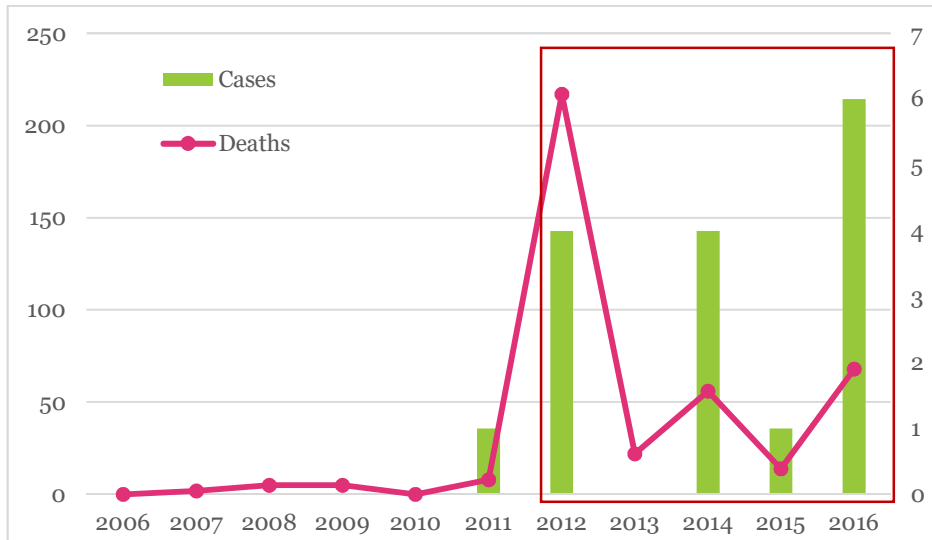
## Problem statement

Incidence of the disease, which was more than a million per year during the first half of the 19<sup>th</sup> Century declined by over 95% during the last three decades due to widespread immunization.<sup>[2]</sup> However, after this sharp decline in cases, there seems to be a plateau in the world incidence of the disease with India contributing as much as 78% of all cases. Because of the vaccine preventable nature of the disease, and initial steady decline, not much attention has been given towards this disease which has not only continued over the past decade in India but has also been 6<sup>th</sup> in the list with highest mortality rate in India. Current statistics show that diphtheria has been re-emerging in India (Fig.1).<sup>[3,4]</sup>



**Fig.1.** Number of reported Diphtheria cases (primary/ left Y axis) and related deaths (secondary/ right Y axis) throughout India during 2006-2016 [CBHI, Govt of India].

Karnataka state has also been reporting a number of cases of diphtheria over the last few years (Fig.2). This is despite a reported increase in immunization coverage. Unfortunately, deaths due to diphtheria has also been on the rise.



**Fig.2.** Number of reported Diphtheria cases (primary/left Y axis) and related deaths (secondary/right Y axis) in Karnataka State during 2006-2016 [CBHI, Govt of India].

Regional Medical Research Centre, (presently renamed as ICMR-National Institute of Traditional Medicine), Belagavi has been carrying out studies on diphtheria in Karnataka with special focus on North Karnataka. The Centre has been receiving isolates from throat swabs for confirmation from various districts of the State from time to time through the District Surveillance Units of the Government of Karnataka. Toxin producing strains of *Corynebacterium diphtheriae* has been identified in many cases and molecular studies has indicated that multiple strains are in circulation in the region (ICMR-RMRC data). Re-emergence of the disease has been documented in the North Karnataka region through research publications (Fig.3) [5,6]. Toxigenic *C.diphtheriae* has also been found from the adjoining districts of the State of Maharashtra (ICMR-RMRC data). Development of resistance to penicillin has been found for the first time in the country which is also a matter of concern [6]. It has been found in most cases of confirmed diphtheria, the subjects either had not been immunized or partially immunized or history of immunization could not be obtained [5,6]. Availability of DAT (anti-poison) has prevented further deaths in outbreak situations [5].

J Med Microbiol 2017;35:247-51.

JMM Case Reports (2014)

DOI 10.1099/jmmcr.0.003558

Original Article

Case Report

Diphtheria outbreak in rural North Karnataka, India

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**Introduction:** The global incidence of diphtheria remained steady during 2007–2011 after a steady decline of over 95 % from 1980 to 2006. This was largely due to a resurgence of the disease in India, which alone accounted for 71–83 % of the total cases reported worldwide.

**Case presentation:** This article describes the identification of an outbreak of diphtheria in two very remote villages of northern Karnataka in South India in May 2011 and detection of further cases in as many as seven nearby villages in the 6 months that followed, which resulted in at least three deaths. The ineffectiveness of the Universal Immunization Programme in its present form in reaching the remote villages is highlighted, and one case of diphtheria with a non-toxigenic strain of *Corynebacterium diphtheriae*, which is very rare in India and has the potential to upset eradication strategies, is documented.

**Conclusion:** This article should provide a wake-up call for the health administrators for restructuring and strengthening immunization strategies and programmes.

**Keywords:** children; diphtheria; outbreak.

Received 30 June 2014  
Accepted 18 August 2014

Resurgence of Diphtheria in Rural Areas of North Karnataka, India

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Abstract

**Background:** A diphtheria outbreak was identified from Vijayapura (formerly Bijapur) district in the South Indian state of Karnataka in 2011. There was a surge in the number of throat swab samples received under the Integrated Disease Surveillance Programme (IDSP) in North Karnataka since then. **Objectives:** A microbiological study was undertaken to generate information on the status of resurgence of the disease in the region. **Materials and Methods:** Throat swabs from 432 suspected cases of diphtheria during 2012–2015 were obtained from government hospitals and primary health centres of 8 districts in North Karnataka and were processed for the culture and identification of *Corynebacterium diphtheriae*. Polymerase chain reaction for the presence of toxin gene (*toxA* and *toxB*) was carried out on the isolates. Antibiotic sensitivity tests were performed on the isolates with a panel of 14 antibiotics. **Results:** Thirty-eight (8.79%) out of 432 samples yielded *C. diphtheriae* on culture. All isolates possessed the diphtheria toxin gene. Out of the 38 confirmed cases, whereas 21 (55.26%) were between 1 and 5 years of age, 14 (36.84%) were aged between 5 and 10 years. Male children were three times more than females in confirmed cases. No information was available on the immunisation status of the cases. Emergence of resistance to penicillin was found with minimum inhibitory concentration reaching up to 6.00 µg/ml. **Conclusion and Discussion:** Our study identified an upsurge in cases of diphtheria in North Karnataka, particularly in Vijayapura District, and to the best of our knowledge, reports the emergence of penicillin resistance for the first time in India. The study calls for enhanced surveillance for the disease, making antidiphtheritic serum available in key hospitals in the region and serves to provide a baseline for future assessment of the impact of the recently launched 'Mission Indradhanush' programme in strengthening Universal Immunisation Programme (UIP).

**Fig.3.** Reports of outbreaks and reemergence of diphtheria in North Karnataka in international and national scientific journals by ICMR-RMRC (NITM), Belagavi, BIMS Belagavi and SSU, Govt of Karnataka [5,6]

Occurrence of cases of diphtheria and associated deaths are often reported (Fig.4) in newspaper articles and in social media.



Fig.4. Recent article in The Hindu, 30<sup>th</sup> July 2017 on diphtheria cases in South Karnataka.

The actual figures of cases of diphtheria and associated deaths is anticipated to be much more than IDSP reports suggest because with lack of diagnostic facilities in most areas, confirmation of cases is not made. Deaths occur mostly because DAT (anti-poison) is not available in most health facilities. In fact, manufacture and supply of DAT is negligible in India. This is again most likely because of the (i) lack of demand, stemmed by lack of awareness of the reemerging status of the disease, and (ii) false sense of security on immunization coverage.

### What is the Root cause?

The root cause of diphtheria reemergence and associated deaths are (i) Dwindling awareness about the reemergence of diphtheria in the post-immunization era (ii) Poor immunization coverage and (ii) Unavailability of DAT.

### Aim/Objectives

- To reduce incidence of diphtheria in Karnataka state.
- To arrest deaths due to diphtheria.

### Gap analysis

Presently, diphtheria control and elimination depends solely upon immunization (UIP). Despite efforts, coverage of DTP3 vaccination in India has officially remained between 80 to 90% for the last 15 years. WHO/UNICEF estimates are lower. At present rate, complete immunization coverage will take several decades resulting in further deaths due to this vaccine preventable disease.

Cases and deaths due to diphtheria can be prevented until complete immunization coverage is reached by ensuring availability of DAT for administration to suspected cases particularly in outbreak sites and vulnerable districts. IEC activities will help increasing awareness and immunization.

## Policy Recommendations

- (i) Ensuring availability of Diphtheria Anti-Toxin (DAT; anti-poison) at all District Hospitals and in CHCs/PHCs where the cases are seen, to prevent deaths.
- (ii) Generation of awareness among communities, health workers, doctors, and health administrators about reemergence of diphtheria, importance of immunization and availability of DAT at District Hospitals through IEC activities.

### Where is DAT available and what is the estimated cost?

DAT can be ordered from select institutions eg. Central Research Institute, (Under the Director General of Health Services, Ministry of Health & FW, Govt of India) Kasauli 173204, Himachal Pradesh. Each vial of 10 ml contains 10000 I.U of DAT. Shelf life of DAT is 2 years. Details are provided in Annexure-I.

Based on confirmed cases during the past 5 years and assuming that all cases require an average of 5 vials of DAT the required number of vials would be 377 and would cost (@ Rs.380/- per vial) approximately Rs. 1.5 lakhs annually.

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## Acknowledgements

The valuable inputs provided by Dr. Suchita Bhattacharya, Freelance Consultant and Visiting Fellow at University of Liverpool, UK, and Prof. Kanchan Mukherjee, Chairperson, Centre for Health Policy, Planning and Management, School of Health Systems Studies (SHSS), Tata Institute of Social Sciences (TISS), Mumbai, is sincerely acknowledged. The kind support of Dr.D.Chattopadhyay, Director, ICMR-NITM and organizational support and coordination of Dr. Rajikant Srivastava, Scientist F & Head of Division of Research Management, Policy, Planning and Coordination, Indian Council of Medical Research (ICMR), New Delhi, is also acknowledged for the timely preparation of this policy brief.

## Annexure- I

### Details of Diphtheria Anti-Toxin (DAT) I.P. (Liquid) and Costs

<http://www.crikasauli.nic.in/page.php?id=21>

**1. DESCRIPTION:**

Diphtheria Antitoxin is a preparation containing the specific globulin having specific activity of neutralizing the toxin formed by *Corynebacterium diphtheria*. It is obtained by purification of hyper-immune serum/plasma of healthy equines.

**2. COMPOSITION:**

Each ml of Diphtheria Antitoxin serum contains:

- Enzyme refined Equine globulin 1000 IU
- Preservative, Phenol 0.25%

**3. STORAGE:**

2 - 8° C in dark and should not be allowed to freeze.

**4. EXPIRY:**

24 months.

**5. TREATMENT / INDICATIONS:**

Diphtheria antitoxin should be administered as soon as the clinical evidence of the disease appears.

Administration of the antitoxin should not await bacteriologic confirmation of the diagnosis since the condition of the patient with diphtheria can deteriorate rapidly.

**6. PRECAUTIONS:**

- Shake well, withdraw the required dose aseptically from the vial
- Do not freeze the contents of the vial
- Protect the constituents of the vial from bright light
- A separate sterile syringe should be used for each individual.
- Allergic reactions with component of product should be borne in mind therefore '**Sensitivity test**' is recommended.

This test is to be performed prior to the administration of DAT as follows:

- Inject 0.1ml of DAT diluted in 1 in 10 in “sterile water for injection (WFI) I.P.” intradermally into the flexor surface of the forearm.
- Inject an equal amount of “sterile water for injection (WFI) I.P.” as a negative control on the flexor surface of the other arm.
- After 30 minutes observe for focal and general reactions. An urticaria wheal, with or without pseudopods, surrounded by a zone of erythema indicates a positive skin test, provided the reaction on the water for injection test is negative.
- In case of negative skin test, the treatment may be started.
- In case of positive skin test, Diphtheria antitoxin may be administered after desensitization and/or under the cover of anti-anaphylactic drugs.

**7. POSOLOGY AND ADMINISTRATION:**

DOSE – As per the recommendation of the physician.

Mild to moderate cases – 10,000 – 30,000 I.U. may be given intramuscularly.

Severe cases – 40,000 – 100,000 I.U. initial portion of the dose intramuscularly and rest intravenously after a gap of 30 minutes to 2 hours.

**8. PRESENTATION:** Each vial containing not less than 10,000 I.U. of the serum.

**9. CONTRAINDICATIONS:**

- Since DAT is a heterologous serum both Type I (anaphylaxis, including urticaria) and Type III (immune-complex) reactions can occur.
- Reaction can occur during or after the treatment even if the skin sensitivity test is negative.
- Anaphylactic reactions can occur even with the test dose. (*Necessary facilities for management of such cases should always be kept ready*).

**10. ADVERSE REACTIONS (IF ANY):**

Immediate or delayed hypersensitivity type reactions may develop with administration of DAT.

Cost: Rs. 380/- vial (10 ml containing 10000 I.U)

[<http://www.crikasauli.nic.in/pdf/pricelist%2005072017.pdf>]

Available from Central Research Institute, (Subordinate Office of Director General of Health Services, Ministry of Health & FW, Govt of India) Kasauli 173204, Himachal Pradesh.

**ROUGH COST ESTIMATES:**

Average reported cases per year in last 5 years from 2012 to 2016: 75.4

Considering recommended of 1 to 10 vials per patient depending on severity, average 5 vials/ patient and a cost of Rs. 380/- per vial, estimated cost will be [75.4 patients X 5 vials X Rs.380 per vial = **Rs.1,43,260/- (Rupees one lakh forty-three thousand two hundred and sixty only) per year.**