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Original Research Article

Resurgence of diphtheria: clinical profile and outcome in a tertiary care hospital of South India

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ABSTRACT

Background: Diphtheria is a potentially fatal acute disease caused by Corynebacterium diphtheria. It was one of the leading causes of mortality in the pre vaccination era. This study is an attempt to highlight the clinical profile, outcome and demographic characteristics, immunization status of pediatric diphtheria cases in South India. Objective of the study was to analyze the clinical profile, immunization status and outcome in children with diphtheria admitted to the PICU in a tertiary care hospital.
Methods: This retrospective study was conducted in a tertiary care hospital in South India. The case records of all children admitted to the hospital between January 1st, 2014 to December 31st, 2018 with clinically suspected diphtheria were analyzed. The data was analyzed with respect to clinical features, demographic characteristics, immunization status, complications and outcome using appropriate statistical methods.
Results: 18 cases were clinically suspected to have diphtheria. The average age of children presenting with diphtheria was 9 years. Out of the 18 cases, 11 were male, 7 were female. 16 out of 18 cases were from rural areas, whereas only 2 cases were from urban areas. Fever, sore throat and dysphagia were the presenting complaints in all cases. Neck swelling, white patch over tonsil and tender cervical lymphadenopathy were the other findings noted. Out of 18 cases, 7 were completely immunized, 8 were incompletely immunized and 3 were not immunized. Antidiphtheritic serum was given in 14 cases. Myocarditis, airway compromise and neurological deficits were the complications noted. Case fatality rate was 50%.
Conclusions: Diphtheria still remains a major public health problem in developing countries like India. Mortality and morbidity due to diphtheria continues to be high despite ready availability of vaccines and antitoxin. Childhood immunization program, especially follow up and administration of booster doses must be prioritized.

Keywords: Diphtheria, Immunization, Myocarditis, Neurological deficits, Outcome

INTRODUCTION

Immunization is a proven tool for controlling and even eradicating disease. An immunization campaign carried out by the World Health Organization (WHO) from 1967 to 1977, eradicated smallpox. Eradication of poliomyelitis is within reach. Since Global Polio Eradication Initiative in 1988, infections have fallen by 99%, and some five million people have escaped paralysis. Although international agencies such as the World Health Organization(WHO) and the United Nations International Children's Emergency Fund (UNICEF) and now Global Alliance for Vaccines and Immunization (GAVI) provide extensive support for immunization activities, the success of an immunization programme in any country depends more upon local realities and national policies. A successful immunization program is of particular relevance to India, as the country

contributes to one fifth of global under five mortality with a significant number of deaths attributable to vaccine preventable diseases. There is no doubt that substantial progress has been achieved in India with wider use of vaccines, resulting in prevention of several diseases. The vaccination coverage at present with EPI vaccines is far from complete despite the long-standing commitment to universal coverage. Though the reported vaccination coverage has always been higher than evaluated coverage, the average vaccination coverage has shown a consistent increase over the last two decades. Increasing trend in vaccine coverage is noted over the last 20 years (Figure 1).

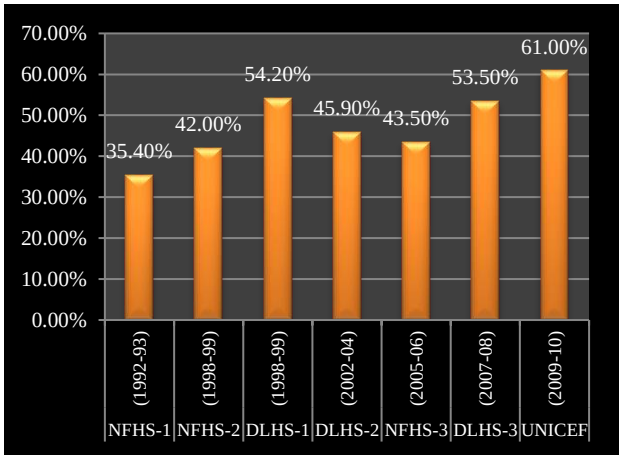

Figure 1: Trends in vaccine coverage.

Table 1: Prevalence of vaccine preventable diseases.

Diseases	1980	1985	1990	1995	2000	2005	2010	2012
Diphtheria	39,231	15,685	8,425	2,123	5,125	10,231	3,123	2,525
Measles	114,036	161,216	89,612	37,494	38,835	52,454	29,808	18,668
Pertussis	320,109	112,416	112,416	4,073	31,431	13,955	38,493	44,154
Polio	18,975	10,408	10,408	3,263	265	66	43	0
Neonatal tetanus	-	9,313	9,313	1,783	3,287	891	373	588
Total tetanus	45,948	23,356	23,356	-	8,997	3,543	1,574	2,404

Source: WHO vaccine preventable diseases : monitoring system 2013 global summary (1)

Table 2: Immunization coverage of different states of India.

State	Full vaccination	BCG	Three doses of DPT	Three doses of polio vaccine	Measles vaccine
Andhra Pradesh	67.1	97.5	79.0	82.1	88.6
Bihar	41.4	81.5	54.4	53.1	54.2
Chhattisgarh	59.3	94.8	71.4	69.7	79.9
Goa	89.8	98.4	91.5	94.1	94.1
Jharkhand	54.1	85	62.6	64.4	70.5
Karnataka	76.7	96.9	84.8	90.3	85.2
Kerala	79.5	99.1	87.1	86.6	87.9
Madhya Pradesh	36.2	84.2	47.4	55.1	57.7
Orissa	62.4	94.2	74.3	78.8	81.1
Pondicherry	80.4	96.6	88.3	88.3	91.1
Rajasthan	48.8	82.8	55.6	63.9	67.5
Sikkim	77.8	98.4	88.7	86.5	92.5
Tamil Nadu	82.6	99.6	90.5	91.1	95.5
Uttar Pradesh	30.3	73.4	38.9	40.4	47.0
West Bengal	75.8	96.2	83.6	83.6	82.8

While gains in coverage proved to be rapid throughout the 1980s, taking off from a below 20% coverage to about 60% coverage for some VPDs, subsequent gains have been limited (Table 1).

Estimates from the 2009 Coverage Evaluation Survey (CES 2009) indicate that only 61% of children aged 12-23 months were fully vaccinated (received BCG, measles, and 3 doses of DPT and polio vaccines), and 7.6% had received no vaccinations at all.[2] Given an annual birth cohort of 26.6 million, and an under 5 year child mortality rate of 59/1000, this results in over 9.5 million under-immunized children each year. There is also a tremendous, heterogeneity in state and district levels immunization coverage in India. In the recent

District Level Health Survey-3 (2007-08) full immunization coverage of children varies from 30% in Uttar Pradesh, 41% in Bihar, 62% in Orissa to 90% in Goa. Tamil Nadu, Kerala, Punjab and Pondicherry have above 80% coverage (Table 2).[3]

An urgent need at present is to strengthen routine immunization coverage in the country with EPI vaccines. India is self-sufficient in production of vaccines used in UIP. As such the availability of the vaccine is not an issue. For improving coverage, immunization needs to be brought closer to the communities. There is need to improve immunization practices at fixed sites along with better monitoring and supervision. Effective behavior change communication would increase the demand for vaccination. There is certainly a need for introducing innovative methods and practices. In Bihar, 'Muskan ek Abhiyan' an innovative initiative started in 2007 is a good example, where a partnership of Government organization, agencies and highly motivated social workers has paid rich dividends. Full vaccination coverage, a mere 19% in 2005 but zoomed to 49% in 2009.[4] Several areas in the national immunization program need a revamp.

Vaccine production by indigenous manufacturers needs to be encouraged to bring down the costs, reduce dependence on imports and ensure availability of vaccines specifically needed by India (e.g. typhoid) and custom made to Indian requirements (Rotavirus and pneumococcal vaccines). The recent vaccination related deaths signal a need for improving immunization safety and accountability and strengthening of an adverse event following immunization (AEFI) monitoring system. Finally setting up a system for monitoring the incidence of vaccine preventable diseases and conducting an appropriate epidemiological study is necessary to make evidence-based decisions on incorporation of vaccines in the national schedule and study impact of vaccines on disease incidence, serotype replacement, epidemiologic shift, etc. Several of the abovementioned issues have been addressed by National Vaccine Policy and mechanism such as National Technical Advisory Group on Immunization (NTAGI) is likely to facilitate evidence-based decisions on new vaccines.[5] Global Vaccine Action Plan (GAVP) signed by 144 member countries of the WHO has also given a call to achieve the Decade of Vaccines vision by delivering universal access to immunization.[6] The GVAP mission is to improve health by extending by 2020 and beyond the full benefits of immunization to all people, regardless of where they are born, who they are or where they live. Immunization is considered among the most cost-effective of health investments. In the United States, cost-benefit analysis indicates that every dollar invested in a vaccine dose saves US$ 2 to US$ 27 in health expenses.[7] There has been improvement in last few years: Introduction of newer antigens in UIP (hepatitis B, 2nd dose of measles, Japanese encephalitis and pentavalent vaccine in many states), framing of National Vaccine Policy, support to indigenous vaccine industry, and acknowledging the need to intensify RI are steps in right direction.[8]

The morbidity and mortality due to diphtheria, tetanus and pertussis has reduced significantly in India since introduction of the whole cell vaccines in EPI. However, coverage with 3 doses of the whole cell vaccine DTwP vaccine is still low (71.5%) and only 41.4% children in the age group of 18-23 months had received first DTwP booster.[9]

Case definitions

Suspected case: In the absence of a more likely diagnosis, an upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and absence of laboratory confirmation; and lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria.

Confirmed case: An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and any of the following: isolation of Corynebacterium diphtheriae from the nose or throat; or histopathologic diagnosis of diphtheria; or epidemiologic linkage to a laboratory-confirmed case of diphtheria.

Completely immunized: who received all dose of DPT vaccine.

Partially immunized: who missed one or more dose of DPT.

Not immunized: one who haven't received any dose of DPT.

Epidemiology

Case fatality rate: The overall case-fatality rate for diphtheria is 5%-10%, with higher death rates (up to 20%) among persons younger than 5 and older than 40 years of age. The use of DTP vaccines has had significant impact at the burden of diphtheria. However, the disease is still persisting in a few states and published reports of the disease do exist in Indian literature indicating outbreaks, secular trends and a shifting epidemiology over the years.[10-12]

Diphtheria

The reported incidence for diphtheria has been 4233 and 2525 cases in the years 2011 and 2012, respectively but underreporting is high likely. The corresponding figures for the year 1980, 1990, and 2000 were 39231, 8425, and 5125, respectively.[13]

Pertussis

In India, the incidence of pertussis declined sharply after launch of UIP. Prior to UIP, India reported 200,932 cases

and 106 deaths in the year 1970 with a mortality rate of <0.001%. During the year 1987, the reported incidence was about 163,000 cases which came down to 40, 508 in 2010 and 39, 091 in 2011 reflecting a decline of about 75%.[14]

The data on pertussis disease and infection in adolescents and adults is sorely lacking. Further, there is no data on Bordetella pertussis infection rates in the community that may be responsible for appearance of typical pertussis disease in infants and children.[15]

Tetanus

The incidence of tetanus in India has also declined sharply from 45,948 cases in 1980 and 23,356 cases in 1990 to only 2,404 cases in 2012.[5] But the worrying part is persistence of neonatal tetanus, and as many as 588 cases were reported in 2012.[13]

Aims and objectives of the study was to assess the clinical profile, laboratory diagnosis and relationship between clinical diphtheria with immunization status and the predictors of mortality and outcome.

METHODS

This is a retrospective observational study, case records of all children admitted to the hospital between January 1st, 2014 to December 31st, 2018 were analyzed.

Inclusion criteria

Clinically suspected cases of diphtheria between the age group of 0 to 14 years, in SDM medical College and Hospital, Dharwad.

Throat swab for Albert's stain and culture sensitivity was sent in all patients under study at the time of admission. Antibiotics and Anti Diphtheritic Serum (ADS) was given in a single dose as recommended. All patients were evaluated for the presence of complications. Demographic data, clinical features, immunization status, treatment, complications and outcome were entered in systematically designed proforma and analyzed. Several variables were compared among the survivors and non-survivors by Chi square test to determine the predictors of mortality.

Exclusion criteria

Cases with ulcero-membranous lesions of tonsil other than diphtheria like, streptococcal phyrungitis, infectious mononucleosis and Vincent's angina were excluded.

RESULTS

During the study period between January 1st, 2014 to December 31st 2018 all children between 0-14 years were analyzed, a total of 18 patients were admitted in PICU with clinically suspected diphtheria, among our study group of patients 61% were male and 39% were female (Figure 2).

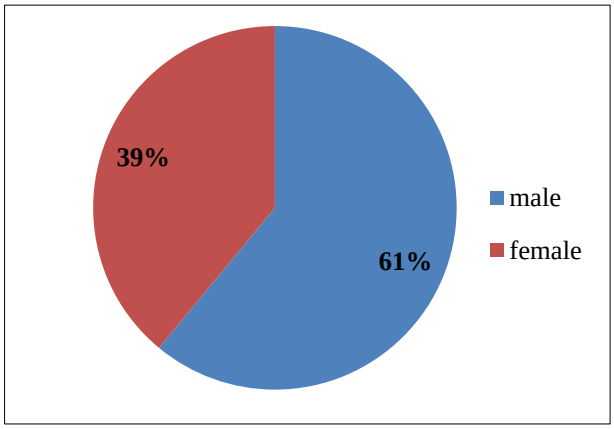

Figure 2: Sex distribution.

In study group 5-10 years children constituted majority almost 2/3rd i.e. 67% followed by 10-14 years 28% and the least by less than 5 years 6% (mean age- 8.72±3.34 years) (Figure 3), among children of our study group 89% belong to rural and very small number 11% belong to urban area (Figure 4).

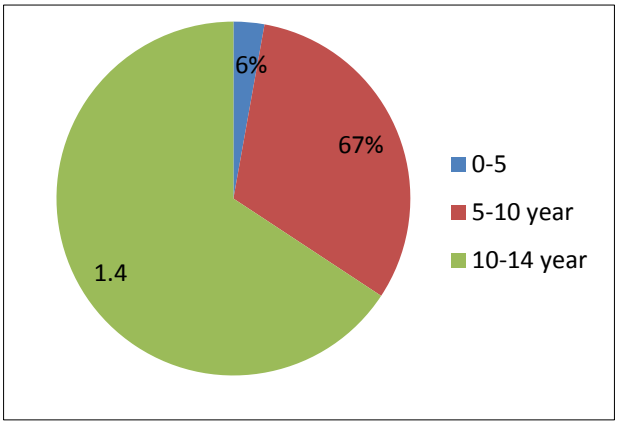

Figure 3: Age distribution.

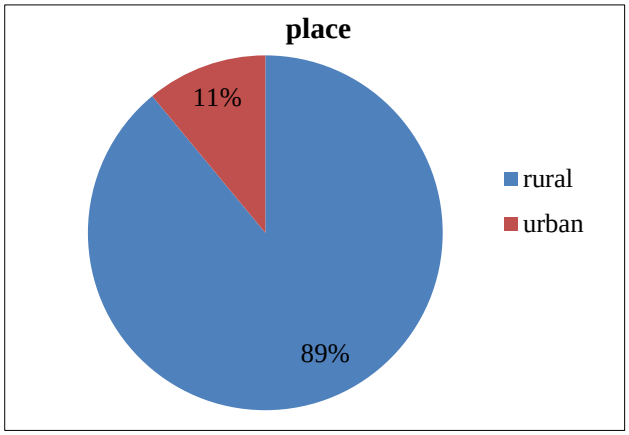

Figure 4: Residence of patients.

Children who presented to the hospital had chief complaint of fever (100%), dysphagia (100%) and throat pain (100%) as predominant symptoms followed by neck swelling in 1/3rd of the patients (33.3%) (Figure 5). On general physical examination of all children in study group (100%) patients had cervical lymphadenopathy on neck examination and throat examination 88% had pseudo membrane (Figure 6).

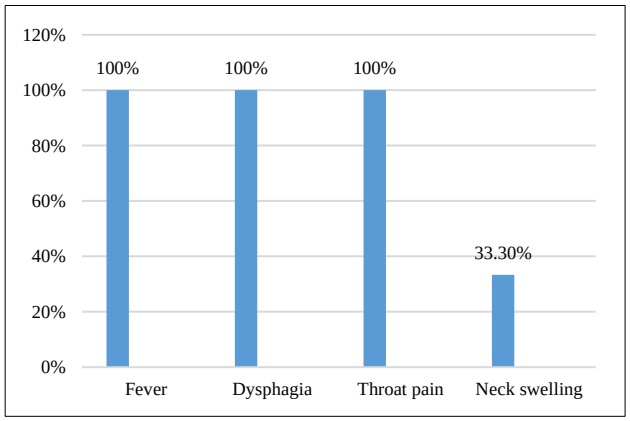

Figure 5: Symptoms at presentation.

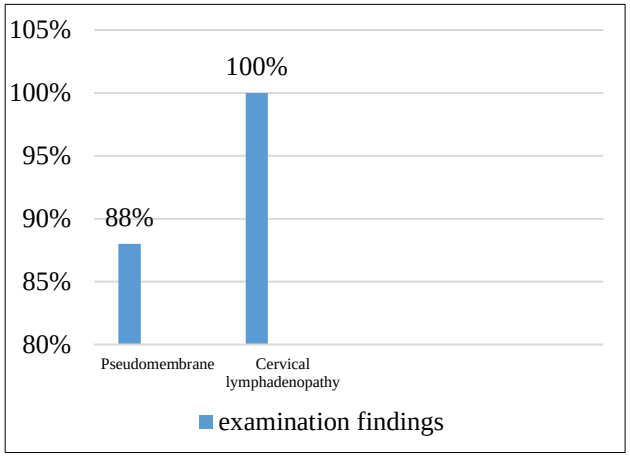

Figure 6: Examination findings.

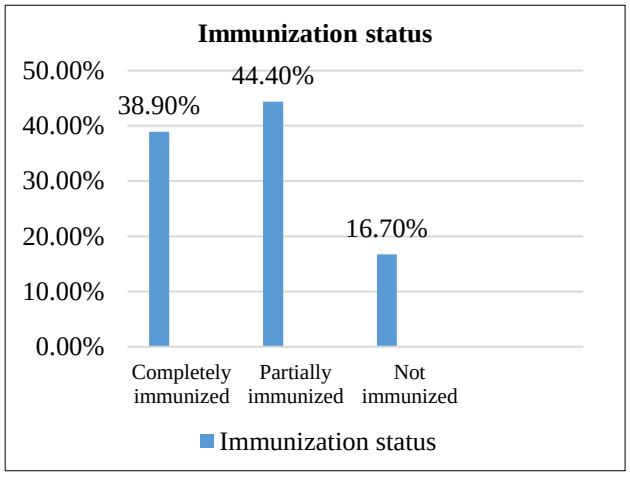

Figure 7: Immunization status of study group.

Among 18 children of our study group enquired about immunization status 38.9% were completely immunized, 44.4% were partially immunized and 16.7% Un-immunized that formed the least who never received DPT vaccine (Figure 7).

In this study group of patients, Albert stain was done of throat swab which showed positive in 83% children and among these 50% of children throat swab culture showed growth of *C. diphtheriae* that constitutes half of study group (Figure 8).

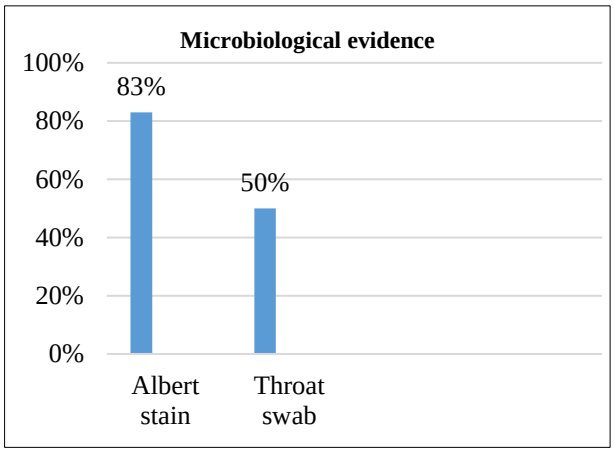

Figure 8: Microbiological data.

Among 18 children of study group, when investigated for complications in the form of 2D echo, cardiac enzymes , arterial blood gas analysis, renal function tests, serum electrolytes, complications noted were myocarditis was most common (72%), followed by airway compromise (55%), kidney injury (27%) and least being post diphtheritic palsy (22%) (Figure 9). Among the study group 50% of children expired and 50% improved (Figure 10). In the present study group presence of myocarditis was most common and was indicator of poor outcome, where all the children with myocarditis expired (Table 3).

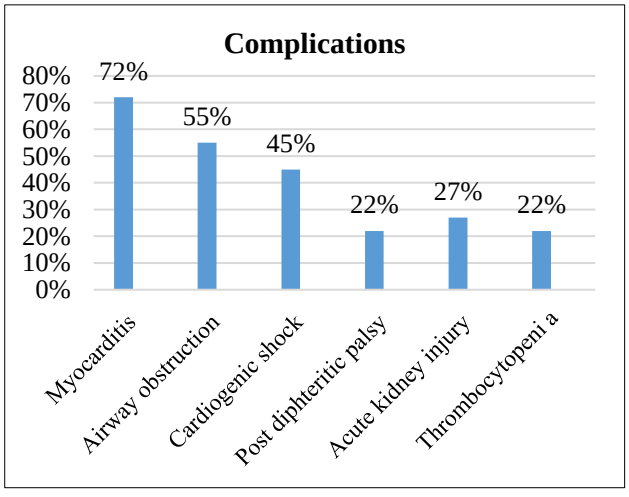

Figure 9: Complications noted.

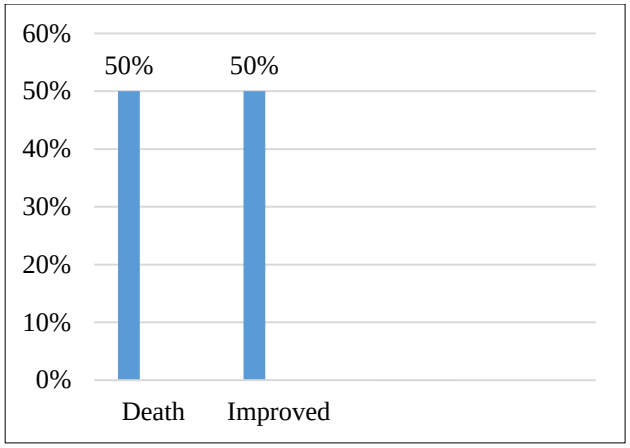

Figure 10: Outcome.

Table 3: Complications noted among the study population.

Complications	Death (n=9)	Recovered (n =3)	p value
Myocarditis	9	4	<0.05
Airway compromise	10	3	0.154
Cardiogenic shock	6	2	<0.05
Acute Kidney Injury	3	2	1
Thrombocytopenia	3	1	0.5

DISCUSSION

Diphtheria, if not detected early and treated promptly with antibiotics and antidiphtheritic serum (ADS), can lead to significant mortality and morbidity because of critical complications such as myocarditis, obstructive airway disease, polyneuritis, cranial nerve palsies, disseminated intravascular coagulation and secondary pneumonia Exotoxin production is dependent on the presence of a lysogenic β-phage, which carries the gene encoding the toxin (tox+).[16,17] The vaccine against diphtheria is given at the second, third and four months, four to five years and 15 to 18 years of age (National immunization schedule).[18]

The Indian state of Karnataka experienced rapid decline in cases of diphtheria along with rest of India and the world as a result of vaccination during the greater part of the past three decades. It reported only 12 cases with no death since 2007. No case was even reported in 2010.[19] The extent to which Vijayapura district is affected is evident from the fact that in the year 2013, it reported 3 of the 5 cases from the entire state of Karnataka while in 2014 it reported 21 of the 56 cases that were reported by the state.[4] However, since 2011, a number of cases had been reported following an outbreak which occurred in the district of Vijayapura, formerly known as Bijapur.[20]

Reasons for poor immunization coverage in India.[21]

- A short supply of vaccines, poor logistical organization.
- Poor screening facilities and postponing vaccination because of minor childhood illnesses.
- Widespread illiteracy and low awareness about the utility of vaccination and vaccine preventable diseases.
- Ignorance about the total doses required.
- Improper or absent counselling.
- Vaccine side-effects.
- Migration of families.
- Lack of effective surveillance system for diphtherias.

Children of 5-10 years age constituted 67% of our study population which was similar to Basavaraj GV et al study (Table 4). Mortality among the cases 50% was similar to other studies (Table 5).

Table 4: Comparison of the most common age of presentation with other studies.

Study	Year	Age group	Percentage
Alakes Kumar et al[22]	2012	5-10 years	40%
Basavaraj GV et al[23]	2016	5-10 years	74%
Vinayaka HS et al[24]	2017	5-10 years	50%
Present study	2019	5-10 years	67%

Table 5: Comparison of the percentage of mortality with other studies.

Studies	Mortality %
Jayashree et al[25]	56.3
Singh SN et al[26]	48
Vinayaka HS et al[24]	45
Present study	50

CONCLUSION

There is an age shift in the occurrence of diphtheria increasingly over 5 years of age. This may be due to several factors like waning immunity with age, lack of booster doses. Resurgence of diphtheria, stresses upon need of improved surveillance and additional booster doses. Occurrence of diphtheria in fully and partially immunized children, questions the cold chain for storage of vaccine. Higher case fatality rates were attributable to delayed referral to higher center, non-availability of ADS.

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Ethical approval: Not required

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