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Research Article

Obstinate diphtheria needs innovation in immunization

Jadab Chandra Sardar[1], Asit Baran Saren[2], Dibakar Haldar[2]*, Kaushik Chatterjee[3], Samar Biswas[4], Tutul Chatterjee[5], Gautam Narayan Sarkar[2]

[1]Department of Community Medicine, R G Kar Medical College, Kolkata, Bengal, India
[2]Department of Community Medicine, Bankura Sammilani Medical College, Bankura, Bengal, India
[3]Department of Gastroenterology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India
[4]Department of Neuromedicine, Bankura Sammilani Medical College, Bankura, Bengal, India
[5]Department of Community Medicine, ID and BG Hospital, Kolkata, Bengal, India

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***Correspondence:**
Dr. Dibakar Haldar,
E-mail: dibahaldar@gmail.com

ABSTRACT

Background: Even after three decades of implementation of the Universal Immunization Programme in India, cases of diphtheria continue to occur in our country with the phenomenon of age shifting. It is pertinent to study the epidemiological determinants of diphtheria. The objective of the study was to profile of diphtheria patients admitted in ID and BG, hospital, Kolkata, Bengal, India.
Methods: A descriptive cross-sectional study was done in September, 2010 involving the diphtheria patients admitted in ID and BG hospital, Kolkata from July, 2009 to June, 2010. Data were collected from BHT of the patients kept in the MRD of ID and BG hospital and telephonic enquiry for those patients whose BHT were found missing of some information, specially immunization.
Results: Almost 90% cases were diagnosed clinically. Majority (47.23%) belonged to 12-29 years age group with clear age shifting. There was rural and female predominance. Almost 2/3rd was unimmunized and more than 3/4th belonged to below poverty level. Patch in throat was the most common clinical feature detected at the time of admission and difficulty in swallowing was the most frequent symptoms. Referral source was unknown for higher proportion of female in ≥12 year who also had higher duration of hospital stay and required significantly higher dose of Anti-Diphtheria Serum. Myocarditis was noted as most frequent complication (41%) and case fatality rate was 3.97%. Peak occurrence was noted during August to November.
Conclusions: Diphtheria seems to be obstinate with age shifting indicating rethinking in our control strategy by universal immunization.

Keywords: Diphtheria, Age shifting, Waning antibody titre, Adult diphtheria vaccine

INTRODUCTION

Diphtheria, an acute toxin induced disease caused by Corynaebacterium diphtheriae can be traced back to 4 BC. Being a prime killer of children it was also known as strangling angel of childhood. It not only results in important complications like post diphtheria Myocarditis, Palatal palsy, Facial paralysis, Bronchopneumonia, Otitis media but also has a case fatality rate of 5% in treated patients.[1] Though the Immunization programme in India started with the aim to reduce vaccine preventable diseases (VPDs) completed three decades in 2008 VPDs are still responsible for over 5 lakh deaths annually in India.[2] Today, India is a leading producer and exporter of vaccines, still the country is home to one-third of the world's unimmunized children.[2] It is mainly due to the reason of suboptimal coverage with the universal immunization programme (UIP) antigens.[3] The evaluated

coverage has been low, the proportion of fully immunized children in India is still at 61 per cent, with wide state-wise, geographical, religion, rural urban and gender variations.[4] Though the UIP has brought down the incidence of diphtheria from 12952 total cases in1987 to 4090 total cases in 2013 (i.e. 68.42% decline) substantial diphtheria cases are still occurring in the country.[5] As per WHO's report India with 6094 cases has contributed 83.2% of global diphtheria cases in 2104.[6]

It has been reported that the bacteria now find their existence among adults and older children who are either unimmunized/partially immunized or possess waning level of antibody titre below 0.01 Lf unit/ml.[7,8] It is a public health menace and concern for immunization strategy against diphtheria giving rise to innovation like extending DPT primary dose up to 7 years of age and DPT 2nd booster at the age of 5-6 years instead of DT.[9]

Infectious disease and Beleghata General (ID and BG) Hospital, Kolkata acts as referral institution for all infectious diseases in West Bengal. Large numbers of diphtheria cases are referred from different parts of West Bengal to the ID and BG.

The present study was an endeavour to describe the profile of diphtheria victims with a view to explore important factors playing behind so that preventive strategy can be revised.

Objectives

- To elicit the sociodemographic and seasonal pattern of diphtheria occurrence.
- To find out the presenting symptoms and the time interval for diagnosis.
- To estimate the duration of hospital stay & amount of Anti-Diphtheria Serum (ADS) required for treatment.
- To describe the complications and case fatality rate of the disease.

METHODS

An institution based descriptive cross-sectional study was carried out in the Department of Community Medicine, ID and BG hospital, Kolkata for a period of three months in the year 2011. The bed head tickets (BHT) of patients admitted in the in-patients department (IPD) are kept in boxes separately for male and females in the medical record department (MRD). For the purpose of unbias selection, at first numbering was done for the male boxes and by lottery one of the boxes was picked up randomly. It contained the BHTs from July 2009 to March 2010. The corresponding box for females was picked up so that the total picture of that period could be revealed. Then lottery was done to select any one between April to June 2009 and April to June 2010.The box containing data from April to June 2010 was found out for male and corresponding female box was gathered to get data for one complete year i.e. from July 2009 to June 2010. Various patients' particular like age, sex, religion, caste, socioeconomic status, residence, referral status, presenting clinical features, amount of anti-diphtheric serum (ADS) received, post diphtheric complications, outcome etc. were collected from the BHTs using a predesigned format. Attempts were made to collect information about the immunization status of those for whom the same couldn't be traced from the BHTs from parents/care givers/patients by telephonic enquiry.

Thus, data for 252 patients were gathered and compiled in Microsoft (MS) Excel sheet and analysed to describe variables by estimating mean, standard deviation (SD), proportion etc. Data display was done using tables and charts. Statistical tests like Chi-square test, Odds ratio (OR) with its 95% confidence interval (CI), Independent't' test etc. were used to draw inference about the relationship between variables.

RESULTS

Most of the cases (89.29 %.) were diagnosed clinically. Altogether 59 (23.41%) throat swab specimens were sent and out of that 45.76% (overall 10.71%) showed growth of Corynaebacterium diphtheriae bacilli and growth of bacteriods was observed in rest.

Table 1: Distribution of diphtheria patients according to age and sex (N=252).

Age (years)	Gender		Total No. (%)	χ2, p value at df1*	OR (95% CI)
	Male No. (%)	Female No. (%)			
<5	23(9.13)	11(4.37)	34(13.49)	31.14, 0.000	4.48 (2.52-7.98)
5-11	40(15.87)	25(9.92)	65(25.79)		
12-29	34(13.49)	85(33.73)	119(47.23)		
30-50	09(3.57)	25(9.92)	34(13.49)		
Total	106(42.06)	146(57.94)	252(100.0)	----------	----------

*First two and last three groups have been clubbed for χ2 test

Analysis showed significant female preponderance in higher age group (Table 1).

Highest number of cases was found in the age group of 12-29 years contributing 47.23%. It indicated the clear age shifting in diphtheria. Male preponderance and female preponderance was noted in less than 12 years and ≥12 years of age groups, respectively.

Average age of upto12 yrs males: 4.52±2.12 and Females: 5.56±2.79 (mean±sd) [t=1.92, p>0.05 at df 97]; Average age of ≥12yrs Males: 24.57±4.5 and females: 25.92±10.7 (mean±sd) [t=1.09, p>0.05 at df 151].

Table 2: Distribution of diphtheria patients according to few sociodemographics (N=252).

Attributes	<12yrs			=>12years			χ2, p at df 1 [OR(95%CI)]
	Male No. (%)	Females No. (%)	Total No. (%)	Male No. (%)	Female No. (%)	Total No. (%)	
Socioeconomic status							
A.P.L [n_1=59]	23 (36.51)	09 (25.00)	32 (32.32)	04 (9.30)	23 (20.91)	27 (17.65)	7.22,0.007[2.23(1.18-4.20)]
B.P.L [n_2=193]	40 (63.49)	27 (75.00)	67 (67.68)	39 (90.70)	87 (79.09)	126 (82.35)	
Religion and caste							
Muslim [n_1=65]	16(25.4)	15(41.67)	31(31.31)	6(13.95)	28(25.45)	34(22.22)	5.26, 0.072* [NA]
SC/ST [n_2=95]	29(46.03)	11(30.56)	40(40.40)	19(44.19)	36(32.73)	55(35.95)	
General caste [n_3=92]	18(28.57)	10(27.78)	28(28.29)	18(41.86)	46(41.82)	64(41.83)	
Residence							
Kolkata [n_1=65]	12 (19.05)	6 (16.67)	18 (19.19)	12 (27.91)	35 (31.82)	47 (30.32)	5.06, 0.080* [NA]
District Urban [n_2=44]	11 (17.46)	9 (25.0)	20 (20.20)	8 (18.60)	16 (14.55)	24 (15.57)	
Rural [n_3=143]	40 (63.49)	21 (58.33)	61 (60.61)	23 (53.49)	59 (53.63)	82 (54.09)	

*at df 2, NA=not applicable

Table 3: Distribution of diphtheria cases as per presenting features & time interval of diagnosis (N=252).

Clinical features at the time of presentation	Duration			Total No. (%)
	<2days No. (%)	2-5days No. (%)	>5days No. (%)	
Fever	26 (10.31)	50 (19.84)	13 (5.16)	89(35.32)
Throat ache	19 (7.54)	34 (13.49)	23(9.13)	76(30.16)
Enlarged tonsil	15(5.95)	11(4.36)	06(2.38)	32(12.69)
Difficulty in swallowing	17 (6.74)	75(29.76)	52(20.63)	144(57.14)
Patch in throat	91(36.11)	60 (23.81)	14(5.56)	165(65.48)
*Others	14 (5.55)	11(4.37)	07(2.78)	32(12.69)

* Bull neck, palatal palsy

Independent't' test established that there was no statistically significant difference in age across the gender in both under 12 years and ≥12 years age groups. Male to female ratio was 1:1.38.

As per the present study 62.3% of the diphtheria patients were immunized (Figure 1).

Majority (56.75%) of cases were from rural settings. It was revealed that the proportion of patient belonged to below poverty level (BPL) category was significantly higher than that of the above poverty level (APL) category in the higher age group. However, no difference in respect of socioeconomic status (SES), religion and residence across the genders could be explored in the two age categories [for SES χ2 values of 1.39 versus 2.87 with p values of 0.24 versus 0.09 at df 1, for

Religion/caste $\chi 2$ values of 3.30 versus 2.97 with p values of 0.19 versus 0.23 at df 1 and for Residence $\chi 2$ values of 0.82 versus 0.48 with p values of 0.67 versus 0.79 at df 1] (Table 2).

The most common presenting clinical feature was patch in throat (65.48%) closely followed by difficulty in swallowing (57.14%). However, about one third also experienced fever (35.32%) as well as pain in throat (30.16%) (Table 3).

Table 4: Distribution of diphtheria patients according to their referral source (N=252).

Source of referral	<12yrs			12yrs+			Total No. (%)
	Male No. (%)	Females No. (%)	Total No. (%)	Male No. (%)	Female No. (%)	Total No. (%)	
Government	18(28.57)	15(41.66)	33(33.33)	22(51.16)	45(40.91)	67(43.79)	101(40.08)
Private	25(39.68)	7(19.44)	32(32.32)	13(30.23)	18(16.36)*	31(20.26)	63(25.00)
Not known	20(31.75)	14(38.89)	34(34.34)	8(18.61)	47(42.73)	55(35.95)	88(34.90)
Total	63(100)	36(100)	99(100)	43(100)	110(100)	153(100)	252(100)

*Reference level for chi-square test between two proportions

Table 5: Distribution of diphtheria patients as per the amount of ADS received (n=252).

Dose of ADS (IU)	Age group (year)						$\chi 2$, p at df 1 [OR(95%CI)]
	<12			≥12			
	Male No. (%)	Female No. (%)	Total No. (%)	Male No. (%)	Female No. (%)	Total No. (%)	
≤20,000[n_1=25]	4(6.35)	4 (11.11)	8(8.09)	6(13.95)	11(10.0)	17(11.11)	2.93,0.087; 1.60 (0.90-2.85)
30,000-40,000[n_2=137]	42(66.67)	20(55.56)	62(62.62)	28(65.12)	47(42.73)	75(49.02)	
50,000-70,000[n_3=75]	15(23.81)	9(25.0)	24(24.24)	9(20.93)	42(38.18)	51(33.33)	
≥80,000[n_4=15]	2(3.17)	3(8.33)	5(5.05)	-	10(9.09)	10(6.54)	
Total [N=252]	63(100)	36(100)	99(100)	43(100)	110(100)	153(100)	----------

Table 6: Distribution of diphtheria patients according to duration of hospital stay (n=252).

Hospital stay (day)	Age group (year)		Total No. (%)	$\chi 2$, p at df 1 [OR (95% CI)]
	<12 (n_1=99) No. (%)	≥ 12 (n_2=153) No. (%)		
<5	-----	*02(1.31)	02(0.79)	**23.69,0.000 [0.27 (0.15-0.48)]**
5-9	07(7.08)	14(9.15)	21(8.33)	
10-14	39(39.39)	101(66.01)	140(55.56)	
≥15	53(53.53)	36(23.53)	89 (37.32)	
Total	99 (100)	153(100)	252(100)	----------

*Both took Discharge at Own Risk Bond (DORB)

Average time interval for diagnosis of: Male < 12 yrs: 3.88±1.63 (mean±sd) days.

Female <12 yrs: 4.01±2.19 (mean±sd) days

Male ≥12 yrs: 4.01±1.29 (mean±sd) days

Female ≥12 yrs: 4.95±1.52 (mean±sd) days

Independent't' test reflected that the male and female patients in younger age groups [t_{97}=0.32, p>0.05] and male between two age groups [t_{104}=0.46, p>0.05] were comparable in respect of time interval between development of illness and admission in I D & B G hospital. However, it was found to be higher among females in higher age group [t_{151}=3.92, p<0.05] compared to their counterpart within same group and females of lower age category [t_{144}=2.41, p<0.05]. It might be due to delay in care seeking from authentic source for the older females.

About one out of every four patients was referred by the government health facility, one fourth from private source. However, referral source was unknown in around one third of cases. $\chi 2$ test revealed that there was no significant difference across the gender in the lower age group [$\chi 2$=4.42, p=0.11 at df 2] so far as the referral source was concerned but the difference was found to be significant in the upper age group [$\chi 2$=8.68, p=0.01 at df 2]. Chi-square test between two proportions of referral from government source versus unknown and private source versus unknown source revealed that source couldn't be elicited for significantly higher proportion of elder females [$\chi 2$=5.45 & 8.06, p=0.019 and 0.004 at df 1; OR=2.87(1.07-7.88) & 4.24(1.25-13.64)] (Table 4).

These might be the cases self-attended or treated and referred by quack to ID and B G hospital.

Table 7: Distribution of diphtheria patients according to complications (n=252).

Complications/outcome	Age group (yrs)						Grand total No. (%)
	<12			≥12			
	Male (n=63) No. (%)	Female (n=36) No. (%)	Total (n=99) No. (%)	Male (n=43) No. (%)	Female (n=110) No. (%)	Total (n=153) No. (%)	
Myocarditis	31(49.21)	13(36.11)	44(44.44)	11(25.58)	48(43.64)	59(38.56)	103(40.87)
Palatal palsy	06(9.52)	04(11.11)	10(10.1)	04(9.3)	09(8.18)	13(8.49)	23(9.13)
*Others	05(7.94)	08(22.22)	13(13.13)	12(7.91)	15(13.64)	27(17.65)	40(15.87)
Death	02(3.17)	01(2.78)	03(3.03)	03(6.98)	04(3.64)	07(4.58)	10(3.97)

*****Encephalitis, peritonsilar abscess, neuropathy

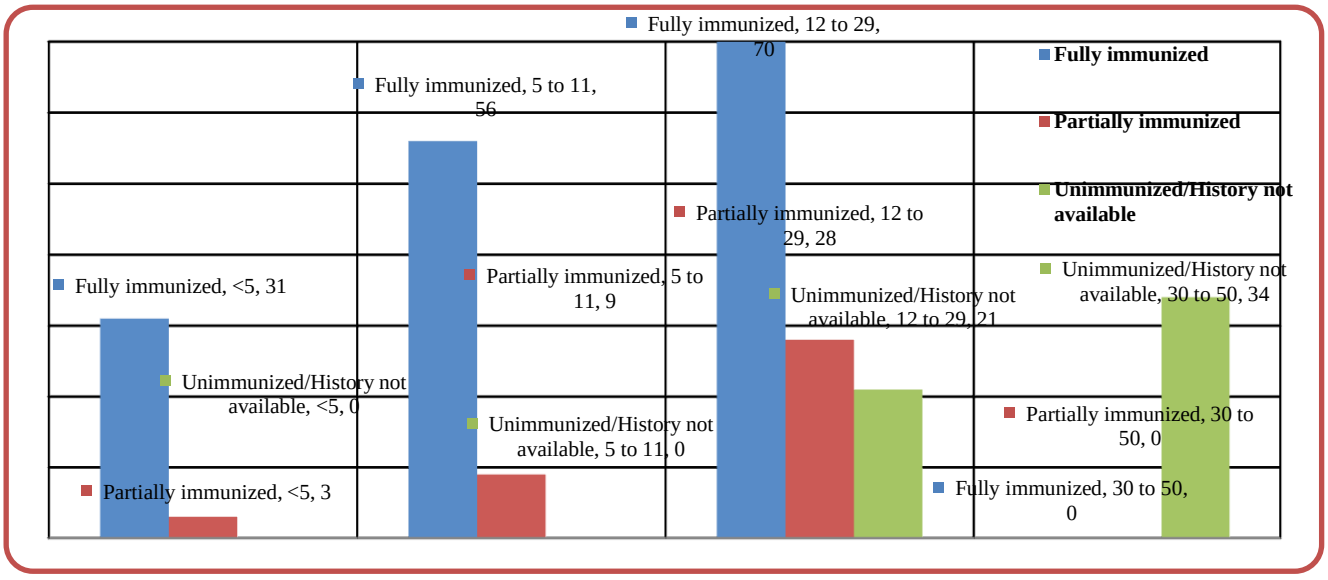

Figure 1: Distribution of cases according to their immunization status.

Almost half (49.02%) of the patients required ADS in the range of 30000-40000 IU, one out of every four patients was treated with ADS of 50000 IU and above. There was no statistically significant difference between the age categories in respect of amount of ADS required for treatment when the doses were categorised <50000 IU and ≥50000 IU. When tested across the gender it was found to exist in the higher age group where the females required higher amount of ADS leaving a statistically significant difference in between [$\chi 2$=0.45 versus 8.95 with p values of 0.506 versus 0.002 at df 1 and OR=1.35 (0.51-3.60) versus 3.39 (1.39-8.43), respectively] (Table 5).

Dose of ADS for <12yrs: Male 27,770±10,954 (mean±sd).

<12yrs: Female 42638±16,888 (mean±sd)

≥12yrs: Male 36,744±5,650 (mean±sd)

≥12yrs: Female 46,590±17,763 (mean±sd)

Higher proportion of patients in the upper age group was shown to have hospital stay more than two weeks and the difference was found to be statistically robust (Table 6).

Average duration of hospital stay for Male <12yrs: 13.38±3.18 (mean±sd) days:

Female <12yrs: 14.06± 4.39 (mean±sd) days

Male ≥12yrs: 13.42±2.18 (mean±sd) days

Female ≥12yrs: 16.37±3.7 (mean±sd) days

Independent't' test revealed that there was no statistically significant difference across the gender within lower age group [t_{97}=0.81, p>0.05] but it was found to exist in the higher age group [t_{151}=6.15, p<0.05] with higher duration of hospital stay among the females. Across the age groups there was no difference between male [t_{104}=0.08, p>0.05] but between female [t_{144}=2.85, p<0.05] groups hospital stay was estimated to be significantly higher among the female of higher age group. So, the female patient pool of higher age group seemed to have more serious illness requiring treatment with higher dosage ADS and for longer duration as well.

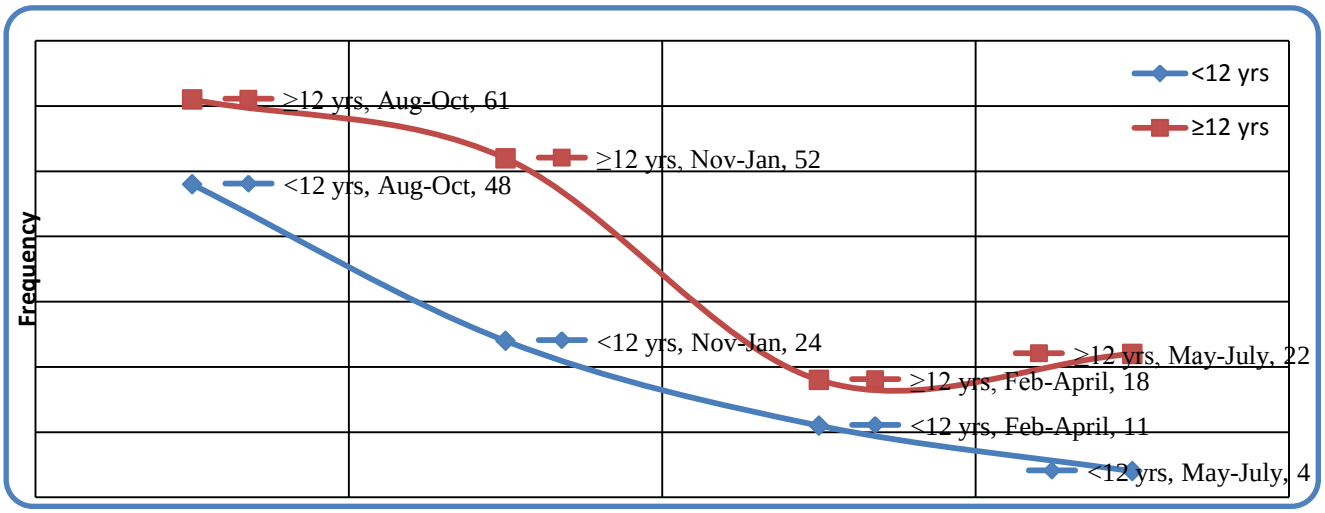

Figure 2: Distribution of diphtheria cases according to time of occurrence in different period of year.

Myocarditis was noted as the most frequent post-diphtheric complication. No statistically significant difference could be observed across two age categories as well as between genders of each category so far as the post-diphtheria complications were concerned. In this study case fatality rate was estimated to be 3.97% (Table 7).

It was revealed from the analysis that most of the cases of diphtheria occurred in the post-monsoon period and then declined steadily in both the age groups (Figure 2). The peak wasn't in the winter contrary to our popular belief.

DISCUSSION

In the current study most of the cases were diagnosed based on clinical criteria, only 10.71% cases were confirmed by laboratory examination. It is with concurrence of what was shown by Nath B et al. who reported 18.18% laboratory confirmed cases in their study in Assam.[10]

This study revealed highest number of cases (47.23%) in 12-29 year age group. Nath B et al also observed that majority (40%) of diphtheria cases belonged to 20-44 years age group, Bitragunta S et al. showed maximum number of cases belonged to children 10–14 years of age.[10,11] Kole AK et al. reported that most common affected age group was children of 5 to 10 years (35%).[12] Basavaraja GV et al. also observed 74.1% cases above the age of 5 years.[13]

There is an age shift in the occurrence of diphtheria recently in our country and 40-45% was above the age of 5 years.[14] This was initially noted in Russian epidemic and China outbreak but however for the first time in India similar observations were made in a study by Sharma NC et al.[15]

This study revealed a female preponderance (57.94%) more specifically, in ≥12 years age group. This might be due to the low nutritional status of our adolescent girls and adult females in both urban and rural areas resulting in low immunity status. However, male dominance (53.33%) was shown by Nath B et al.[10]

Bitragunta S et al. reported higher number of girls and women patients.[11] Kole AK et al. observed male preponderance of cases below 10 years, whereas female preponderance was seen above 20 years.[12]

Basavaraja GV et al. also noted in their study that females (51.6%) over numbered the males.[13] In contrast Maheriya KM et al. reported male dominance with 1.833:1 male to female ratio.[16]

As per current study, 62.3% of patients were reportedly fully immunized compared to 75.0%, 48.3% and 15.79% stated by Kole AK et al., Basavaraja GV et al. and Maheriya KM et al., respectively.[12,13,16]

Analysis reflected that higher proportion of diphtheria patients belonged to BPL category which could be attributed to the fact that rural patients outnumbered their urban counterpart which in turn might be because rural population constitutes almost of 70% of our population. Poor immunization coverage in rural area as well as low environmental condition and nutritional status arising out of lower socioeconomic class favoured transmission and persistence of Corynaebacterium diphtheriae among their community. Kole AK et al. found 50% of the diphtheria patients belonged to lower socioeconomic status.[12] Maheriya KM et al. reported 47.0% rural cases and 76.3% from lower socioeconomic class.[16]

Peak in autumn as revealed from current study was also observed by Maheriya KM et al. who reported that great number of increase was seen during month of August to month of December.[16] However, Bitragunta S et al. to the contrary observed that diphtheria cases occurred throughout the year with lower incidences during July and August.[11] Other studies also stated that peak is usually in the month of August to November.[17-19]

In this study the most common presenting clinical feature was patch in throat (65.48%) closely followed by difficulty in swelling (57.14%). However, about one third also experienced fever (35.32%) as well as pain in throat (30.16%). Kole AK et al. observed pain in throat and fever in 74% and 56% of cases.[12] Maheriya KM et al. reported that pain in throat and fever were universal.[16]

Current study revealed Myocarditis as the most common complication observed in 40.87% of cases compared to a higher rate of 68% cases reported by Kole AK et al.[12]

The current study reported low case fatality rate of 3.97% which was concurrent to 3.33%, 1.2% and 2.5% reported by Nath B et al, Bitragunta S et al. and Kole AK et al.[10-12] In 2013, India experience case fatality rate (CFR) of 2.61% for diphtheria.[5] However, higher rates of 41.0% and 23.67% were shown by Basavaraja GV et al. and Maheriya KM et al.[13,16] The higher CFR was due to delayed treatment, specially with ADS.

The elder females were found to suffer the most as evident by longer duration of hospital stay and requiring higher dose of ADS for treatment. It might be due to care seeking from unauthorised care provider in earlier part of illness resulting in delay in admission in hospital via self-reporting which might be reflected from the fact that referral source couldn't be traced for higher proportion of them.

Persistence of diphtheria with its age shifting in India once again is reaffirmed in this study and calls for rethinking on the part of the policy makers to innovate changes in vaccination strategy against it. Universal immunization through Behaviour Change Communication (BCC), utilizing missed opportunity, monitoring of UIP are the need of the hour. The immunization is to be strengthen with new initiative to achieve 90% coverage of children with DPT and 75% coverage of adults with dT vaccine as suggested by Eskola J et al. and administration of the second childhood booster at 9 years instead of 6 years as proposed by Vitek CR.[8,20] Or booster doses with dT may be thought of at 10 years and 16 years instead of tetanus booster only.

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