Factors associated with persistence of diphtheria at Hyderabad, Andhra Pradesh, India 2006

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Dissertation project submitted in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology (M.A.E) of

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CERTIFICATION

This is to certify that this dissertation, titled **'Factors associated with persistence of diphtheria at Hyderabad, Andhra Pradesh, India, 2006'**, submitted by Dr. B.Sailaja, in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology, is the original work done by her and has not been submitted earlier, in part or whole, for any other publication or degree.

Date 26.02.07

Director

Table of contents

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ABSTRACT:

Background: Andhra Pradesh accounted for half of global diphtheria cases in 2005 and Hyderabad accounted for 16% of state cases. We conducted a study to understand whether diphtheria persisted because of vaccine failure or failure to vaccinate.

Methods: All diphtheria case-patients in Hyderabad are referred to the Fever hospital. We described cases hospitalized during 2003-2006 by time, place and person. We prospectively compared laboratory-confirmed cases aged 10 years and less with neighborhood matched controls to estimate vaccine efficacy. We surveyed children aged 12-23, 18-36 and 54-72 months to estimate coverage for primary vaccination, fourth (18 months) and fifth (54 – 72 months) diphtheria doses.

Results: 2,685 cases were admitted in 2003-2006 (annual attack rate: 17/100,000, (case fatality: 1%, median age: 17 years). Attack rates were highest in children aged 10-14 years, women and among religious minority (28, 19 and 68/100,000, respectively). Four divisions of Hyderabad with large proportion of Muslim population had 90% of cases. Cases occurred throughout the year with a lower incidence during July and August. Among children aged five years or more, five doses were 91% (95% CI=67-98) efficacious. The coverage for primary vaccination, fourth and fifth doses was 90% (95% CI: 86.3-93.2), 60% (95%CI: 53.7-65.6) and 33% (95% CI: 27.3-40.1) respectively. Compared with others, the Muslims had a coverage that did not differ for primary vaccination but that were lower for the fourth and fifth doses (coverage ratio: 0.9, 95% CI: 0.9-1.1, p=0.03 and 0.6, 95% CI: 0.75-0.95, p=0.000 respectively).

Conclusions: Receiving booster dose was key for diphtheria protection. However, coverage dropped after primary vaccination, especially among a minority with higher attack rate. We recommended increasing the booster doses coverage with an emphasis on minorities.

LIST OF TABLES AND FIGURES

INTRODUCTION

Diphtheria is a disease caused by the exotoxin produced by *Coryebacterium diphtheriae*. Diphtheria is an upper-respiratory tract illness characterized by sore throat, low-grade fever and an adherent membrane (pseudo membrane) on tonsils/pharynx and/or nose. Diphtheria toxin affects the myocardium, nervous and adrenal tissues causing cardiac failure and paralysis[1]. Globally, diphtheria was a major cause of childhood mortality in the pre-vaccination era[2]. The incidence of diphtheria in the developed nations has steadily declined following effective immunization programs since the 1920's[3]. In the late 1970s, the World Health Organization's (WHO's) Expanded Programme on Immunization (EPI) strengthened childhood immunization in developing countries[4]. As per the WHO/EPI schedule, the primary series of DPT-(diphtheria, pertussis and tetanus) is administered in 3 doses, starting as early as 6 weeks of age and given with a minimum interval of 4 weeks. Where resources permit, additional doses can be given after the completion of the primary series[5]. Many national immunization programmes including the Universal Immunization Programme of India offer 2 booster doses, one at 18 months of age years of age and a second during 54 and 72 months. Vaccination coverage of more than 80% is recommended for the herd effect[5].

After three doses of primary immunization, 94% to 100% of children develop antibodies above the protective titre of 0.01 IU/ml[2, 6-9]. Case-control studies carried out during the epidemic in the 1990s in countries of the former Soviet

Union also showed that the protective efficacy of three doses of vaccine among children aged <15 years ranged between 97-98%[10,11]. However, without booster immunizations toxoid-induced immunity drops below protective levels[2,12]. This might lead to an increasing proportion of adults in countries with long-standing diphtheria immunization programs to become susceptible[2,12].

Following the introduction and widespread use of diphtheria toxoid-containing vaccines, the incidence of diphtheria and the circulation of toxigenic *Corynebacterium diphtheriae* decreased in industrialized countries. However, a re-emergence of the disease was reported in selected industrialized countries, including Netherlands, Norway and Germany that was largely attributed to waning vaccine immunity after adolescence and importation of cases from the endemic developing world[13]. The outbreak in the former Soviet union during 1990-1996 that affected 157,000 people and caused 5,000 deaths was largely attributed to decrease in childhood vaccination coverage, increase in adult susceptibility, changes in childhood vaccination practices, mass population movement due to political unrest and changes in the predominant strain of C. diphtheriae[14-19]. In developing countries, the incidence of disease declined substantially during the 1980's after introduction of immunization[20]. The disease however did not completely disappear because of insufficient vaccination coverage, poor socio economic conditions, over crowding and sub-optimal vaccine efficacy[21].

Of the 8,229 diphtheria cases reported globally to the World Health Organization (WHO) in 2005, 5,826 (71%) cases were from India[22]. Of these, 4,161 (71%) were from the state of Andhra Pradesh[23]. Diphtheria remains an important public health problem in Hyderabad, the state capital. In the year 2005, 663 (16%) of the cases reported from the state were from the city[24]. The reported administrative coverage (i.e., the number of doses administered divided by the target population) for primary diphtheria vaccination was 100% from 1995 to 2004[25], and 98% in 2005-06 in Hyderabad[26]. In addition, in 2005, the reported coverage for the first and second diphtheria booster dose was 89% and 63% respectively[26].

We conducted a study to understand whether diphtheria persisted in Hyderabad because of vaccine failure or failure to vaccinate. The objectives of our study were to (1) describe the distribution of diphtheria cases in Hyderabad in terms of time, place and person, (2) describe the clinical characteristics of patients, (3) estimate the coverage for the various doses of diphtheria vaccine and (4) estimate the vaccine efficacy.

METHODS

Descriptive epidemiology

All diphtheria patients identified in Hyderabad and neighboring districts are admitted to the Fever hospital (Sir Ronald Ross Hospital) of Hyderabad. We included diphtheria cases admitted during 2003-2006 among residents of Hyderabad in the study. We reviewed medical records to extract information regarding demographic variables including age, sex, religion, month and year of occurrence and circle (i.e., administrative sub-division) of residence.

Clinical characteristics

We prospectively collected information about clinical characteristics of diphtheria patients admitted between 1 July and 30 November 2006. We collected information regarding signs and symptoms, laboratory results for smear and culture, treatment administered complications and outcome using standardized, close-ended chart abstraction form.

Case control study

We conducted a prospective, case-control study between 1 May and 30 November 2006 to estimate the vaccine efficacy and identify risk factors for illness. We defined a case of diphtheria as (1) an acute febrile illness with throat pain and grayish white patch on the tonsil, fauces or pharynx with (2) laboratory confirmation through a positive throat smear or culture. We included all cases of diphtheria among patients 10 years of age or younger who resided in Hyderabad admitted in Fever hospital during May and November

2006. We recruited all the cases admitted during the defined period in the hospital and selected age and residence matched controls from the community. We collected information about religion, educational status of the parents, monthly family income and the number of doses of diphtheria vaccine received through interviews of mothers or guardians for case-patients and control-subjects. We ascertained the vaccination status of a child from the vaccination card when it was available. When a card was not available, we considered the number of doses reported by the mother or guardian. Assuming odds ratio of 3, ratio of cases to controls as 1 and the exposure among controls as 10%, the sample size was calculated as 112 with 95% confidence interval and power of 80%.

Vaccination coverage

We conducted three cross sectional surveys in the city among children aged 12-23 months, 18 to 36 months and 54 to 72 months of age to estimate the coverage of primary vaccination, fourth and fifth dose of diphtheria, respectively. We stratified the sample for the seven circles of Hyderabad. We took eleven clusters of children in each stratum for each age group using cluster-sampling methods. We selected clusters with a probability proportional to size. We used the lot quality assurance sampling (LQAS) methods[27] to (1) estimate the sample size and (2) analyse the data.

We considered 20% (P_0) as the upper threshold of incompletely immunized children beyond which intervention of health system is deemed necessary. The lower threshold (P_a) was considered 8%. Using the Lemeshow and Taber LQAS tables[27], with an alpha error of 1% and power of 80%, the lot sample size needed was found to be 94, and the minimum number of incompletely vaccinated children (d) that would be accepted was 9. We selected 94 children in each of the three age groups from the seven strata (circles) in Hyderabad. Our null hypothesis was that immunization coverage in each circle for each age group is between 80% and 92%. For each age group, and in each stratum, if the number of incompletely vaccinated children was 9 or less, we accepted the null hypothesis that the proportion of completely vaccinated children is more than 80%. Alternatively, if the number of incompletely vaccinated children was more than 9, we rejected the null hypothesis that the proportion of completely vaccinated children is more than 80%.

We ascertained the vaccination status using vaccination cards. When the card was not available, we used mothers' history to know the number of doses of diphtheria vaccine received. For the children who received the vaccine from urban health centres in Hyderabad, we crosschecked the mothers' history from field worker's health records. The field worker of the area accompanied the team with her field register and the register was checked when the immunization card was not available and the vaccine was taken at the Urban health centre. In case of discordance, and the child received an extra dose at a place other than the urban health centre, we accepted mother's history. If the vaccine was taken at urban health centre and there was discordance about the number of doses received, the field worker's record was accepted. We used three criteria for defining a completely vaccinated child according to the age group. First, for children between 12 and 23 months of age, we defined it as having received three primary doses of DPT. Second, for children between 18 and 36 months of age, we defined it as having received four doses of DPT (three primary doses and a first booster). Third, for children between 54 and 72 months of age, we defined it as having received five doses of diphtheria-containing vaccine (three primary doses, first and second booster dose). We also collected information about the source of vaccination, religion and reasons for non-vaccination (when applicable) from mothers or guardians.

Data analysis

We calculated the incidence rates of diphtheria by age and gender. We drew a map of the incidence rate by circles. We plotted the attack rates over time to assess the trend between 2003 and 2006 and to describe the seasonality. We calculated the frequency of clinical findings among the patients admitted between 1st July and 30th November.

For the case control study, we compared the results of a matched and unmatched analysis for the calculation of odds ratio. After having checked that breaking the match did not affect substantially the strength of the association for the vaccine doses, we calculated the odds ratio for incremental doses of vaccination in two different strata: the under fives and the five years of age and older. Then, we included all exposures, including vaccine doses, in a stepwise conditional logistic regression using EPI Info (CDC, Atlanta). The number of diphtheria vaccine doses received was factored in the analysis so that the strength of the association could be calculated independently for each dose. Other variables entered in the model were dichotomous. We calculated the vaccine efficacy (%) on the basis of the matched and unmatched analysis as 1- odds ratio[28]

We conducted two analyses of the coverage survey: A LQAS analysis by strata and an overall analysis. Firstly, we accepted the null hypothesis that the immunization coverage in each circle for each age group is between 80% and 92%, if the number of incompletely vaccinated children (d) was less than or equal to 9 with a probability of 99% and power of 80%. Alternatively, the coverage was considered to be not more than 80% if d was more than 9.

Second, for the overall analysis, we calculated the proportion of completely immunized children for the three age groups in Hyderabad city after weighting the estimated number of children in these age groups in each circle. We also calculated the pooled immunization coverage separately for Muslims and non-Muslims.

Human subject protection:

We obtained the informed consent from the parents. The identity of the child/patient was coded to retain the confidentiality. The participants had the benefit of completing their vaccination schedule if they had not completed it. We obtained the clearance from the Institutional Ethical Committee of National Institute of Epidemiology, Chennai. We obtained the permission to carry out the study from the Commissioner, Family Welfare, Andhra Pradesh, Director of Health, Andhra Pradesh, District Medical and Health Officer, Hyderabad and Medical Superintendent, Fever Hospital, Hyderabad.

RESULTS

Descriptive epidemiology

During 2003-2006, 2,685 cases of diphtheria were admitted in the fever hospital, Hyderabad. Overall 28 patients died (case fatality: 1%). The reported incidence rates increased from 11 per 100,000 in 2003 to 23 per 100,000 in 2006 (χ^2 for trend=151.9, p=0.0000). The median age of case patients was 17 years (range: 9 months-80 years). Attack rates were lowest among infants and increased with age to reach a maximum among children between 10 and 14 years of age (Table 1). Attack rates were higher among females. 1,874 of the cases (70%) occurred among Muslims. Cases of diphtheria occurred throughout the year with a lower incidence during July and August (Figure 1). Attack rates in circles ranged between 17 and 25 per 100,000 and were highest in the first four circles (Figure 2). These first four circles accounted for 90% of cases in 2003-6.

Clinical features

361 patients with diphtheria were admitted at the Fever Hospital between 1st July and 30th November 2006. Fever (91%), throat pain (94%) and enlarged tonsils (81%) were most common clinical features. 80% of patients had characteristic greyish white patch (pseudo membrane) of diphtheria on tonsils (

Figure 3).

The median duration between onset of symptoms and hospitalisation was three days (range: 1-30 days). Patients were hospitalised for a median duration of six days (range: 1 - 67 days). The diagnosis of diphtheria was confirmed in 294 (81%) cases (276 positive throat swabs and 85 positive cultures). The ECG of 17 (4.8%) patients was suggestive of myocarditis. All the patients were treated with crystalline penicillin, gentamicin and L-carnitine. Anti-diphtheritic serum was not administered, as it was not available. Nine of the 361 cases died (Case fatality rate: 2.5%). Out of the 361 patients, five patients (1.4%) reported history of exposure to diphtheria patients at home. Fourteen (4%) patients reported that they had suffered from diphtheria previously.

The patients admitted with diphtheria were administered three doses of diphtheria vaccine; first dose at the time of discharge, a second a month later and a third after six months. Close family contacts of the patients were also administered three doses of diphtheria vaccine.

Case control study

Of the 139 children aged 10 years and less admitted for diphtheria between May and November 2006, 123 (88%) fulfilling the case definition were included in the case control study. The median age of cases was seven years and 62 (50%) were female. On univariate analysis, odds ratio for diphtheria was significantly higher among Muslims (OR=3.2, 95%CI=1.5-7.9). Compared to unvaccinated children, odds ratio for acquiring diphtheria was significantly lower among those who received diphtheria vaccine (OR=0.4, 95% CI= 0.2-0.9).

When stratified for age (<5 and ≥ 5 years), crude vaccine efficacy of three and four doses of diphtheria among under-five children was 88% (95% CI= 0-100%) and 90% (0-100%) respectively. Among children aged five years or more, crude efficacy of the vaccine increased from 22% (95% CI=0-70) for three doses to 40% (95% CI=0-78) for four and 84% (95% CI=48-95) for five doses (Table 2). As the number of case patients under five years was too small, we restricted the conditional logistic regression analysis to children aged 5 years and more. When adjusted for religion, family income and literacy status of parents, the risk of diphtheria was significantly low among individuals who received five doses of vaccine (OR=0.08, 95% CI=0.02-0.32) (Table 2).

Coverage survey

LQAS analysis: The number of incompletely vaccinated children exceeded the critical value of nine in all the three age groups and all the lots, except for circles three, five, six and seven where it was 9, 6, 8 and 2 respectively among children 12 to 23 months of age. Thus, coverage of complete primary vaccination could be considered to between 80-92%, with a one percent risk of error in these four circles (Table 3), whereas the coverage in the remaining three circles not could be more than 80%. The coverage for boosters in 18-36 months and 54-72 months age groups could not be considered to be more than 80% in all the lots. Among the children aged 12-23 months 466/658 (71%) had immunization cards, amongst the 18-36 months ages 450/658 (68%) had immunization cards and among the 54-72 months age children 253/658 (39%) had immunization cards.

Of the 194 mothers whose children were not vaccinated, 93 (48%) lacked the information, 62 (32%) did faced obstacles in vaccinating their children and 39 (20%) lacked motivation for completing the vaccination schedule. Among the 93 mothers who lacked information, 46% were not aware of the need to return for the next dose, 29% were not aware of the need for immunization and 17% were not aware of the time and place of immunization. Among the obstacles faced by the mothers of incompletely vaccinated children, 35% of children were ill and not brought for vaccination and 46% of the mothers were too busy or had family problems. Of the 20% mothers who lacked motivation 59% had postponed vaccination and 18% believed in rumors. Out of the total 1974 children sampled for immunization coverage 1619 (82%) received vaccination from the public health sector.

Overall coverage: The weighted vaccination coverage of primary immunization among children aged 12-23 months was 90% (591/658, 95% CI=86.3-93.2. Weighted average for the first booster of the children aged 18-36 months was

60% (396/658, 95% CI=53.7-65.6. Among children aged 54-72 months 33.7% (235/658, 95% CI=27.3-40.1) had received five doses of diphtheria vaccine.

The pooled coverage of primary immunization among Muslim and non-Muslim children aged 12-23 months was 86.7% (194/223, 95% CI=80.3-93.3) and 91.6% (397/435, 95% CI=88.0-95.3) respectively. The proportion of children who received the four and five children among Muslims was 54.2% (122/225, 95% CI=43.8-62.9) and 24.4% (53/217, 95% CI=16.5-33.3) respectively. The corresponding coverage for non-Muslim children was 63.3% (274/433, 95% CI=55.3-71.5) and 41.3% (182/441, 95% CI=31.1-47.1) respectively. Compared with others, the Muslims had a coverage that did not differ for primary vaccination (coverage ratio: 0.95, 95% CI: 0.90-1.1, p=0.11). However, the coverage for the fourth and fifth doses was significantly lower among Muslim children (coverage ratio= 0.86, 95% CI: 0.75-0.99, p=0.03, and 0.59, 95% CI: 0.5-0.8, p=0.0000, respectively) (Table 4).

DISCUSSION

Diphtheria continues to be endemic in Hyderabad. Attack rates increased between 2003 and 2006, predominantly affecting children aged 5-14 years, women and Muslims. The rates of diphtheria were highest in four of the seven circles in the city. Among children aged five years and older, diphtheria vaccine was efficacious among those who received five doses. The coverage of primary immunization was low in three out of seven circles whereas the coverage for first and second boosters was uniformly low in all the circles of the city. While the coverage for the primary immunization was similar among Muslims and non-Muslims, the coverage for the booster doses dropped down among Muslims.

In Hyderabad, the age-specific attack rates were lowest among infants. Thereafter attack rates increased among children aged 2-4 and 5-9 years. About 59% of the diphtheria cases in Hyderabad occurred among adolescents and adults. We did not assess the population immunity against diphtheria, but occurrence of cases among adolescents and adults groups suggests low levels of immunity. This may be on account of low overall vaccination coverage among children or waning of the vaccine induced immunity. In the countries where diphtheria re-emerged after successful control with vaccination, adolescents and adults were increasingly affected on account of waning of vaccine-induced immunity in the absence of periodic booster doses and natural infection[29].

Nearly three fourth of the diphtheria cases occurred in Hyderabad were among the Muslims. Attack rates were higher in the first four circles of the city where the proportion of Muslims is also higher (range:25%-85%). Though primary vaccination coverage among Muslims was not different from the non-Muslims, coverage for the boosters was low. The booster doses were more effective in protection against diphtheria in our study. Thus, the higher attack rates in first four circles might be on account of low booster coverage among the Muslims who are in higher proportions in these circles. In the past four years, an increasing trend was observed in the incidence of diphtheria. This may be on account of increasing number of susceptible over the years due to low vaccine coverage. Low vaccination coverage was also observed during the National Family Health Survey-II in the year 1998-99 (DPT3 coverage of 79.5%)[30]. WHO-UNICEF estimate for DPT3 coverage for the year 2005 is 59%[31].

The efficacy of diphtheria vaccine among the under-five children in Hyderabad was comparable with other studies[10-11,32,33]. Among children aged five years or more, vaccine efficacy of 91% was observed for those who received all the five doses of the vaccine. However, efficacy with three or four doses of vaccine was lower than the reported efficacy in other countries[10-11]. Case-control studies carried out among children during the diphtheria epidemic in former Soviet Union showed that three or more doses of the vaccine induced protective efficacy between 97% (95% CI= 94.3-98.4)[10] and 98.2% (95% CI=90.3-99.9)[11]. Protection increased to 99.7% with four and 99.9% with five doses[10-11]. The lower efficacy observed in our study could be due to non-differential misclassification in assessing the vaccination status. We collected information about vaccination status based on vaccination card and mothers' history if the card was not available. Only 16.3% of the controls and 19.5% of the cases had vaccination card. Lower efficacy could also be on account of problems associated with cold chain. However, evaluation of universal immunization programme in Hyderabad did not identify any gaps in cold chain maintenance at the district or at the urban health centres where majority of the children are vaccinated. The findings of the study thus suggest that both the boosters are essential to confer protective immunity among children aged five years or more.

A higher attack rates among Muslims was observed in our study that may be on account of lower coverage of boosters among them. In the state of Uttar Pradesh in India, occurrence of poliomyelitis cases among Muslims was attributed to low community acceptance of pulse polio immunization[34]. In contrast to Uttar Pradesh, the vaccination was acceptable to Muslims of Hyderabad, as the coverage for primary immunization among Muslim children was comparable to non-Muslims. However, there was a significant difference between Muslim and non-Muslims with respect to the coverage for diphtheria booster doses.

Lack of awareness among mothers regarding the need to return for the booster and obstacles like illness of the child or family members were the main reasons cited by the mothers of incompletely vaccinated children. Lack of information with regards to the necessity of booster doses and the schedule may be improved by increasing the inter-personal communication between the health providers and mothers. Minor ailments of the child that are considered as obstacles to immunization by the mother can be removed by educating the mothers. The health system at Hyderabad is functioning with sub-optimal number of field staff[35]. The over-worked health workers do not spend sufficient time communicating with the mothers about the next dose of vaccine. The immunization schedule is printed on the card and on the walls of the all health centres but personal communication may be helpful as average literacy rate is low.

The coverage of primary immunization in three of the seven circles and coverage of first and second booster in all the circles was less than 80%. Overall immunization coverage of diphtheria declined from 90% for three primary doses to 60% for the first and 33% for the second booster. The coverage of fourth and fifth dose of the vaccine was low in all the circles of Hyderabad. Significantly higher proportion of Muslim children did not receive the fourth and fifth dose of the vaccine. Universal immunization programme has been in place in Hyderabad since 1985. The programme emphasizes universal coverage of BCG, three doses each of DPT and OPV, measles and hepatitis B among infants and

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Our study had several limitations. First, we included all the admitted cases of diphtheria in Fever Hospital, Hyderabad. Milder cases that might not have reported to the hospital were not considered for describing the situation of diphtheria. Second, the vaccination cards were available for only 1169 (59%) of 1974 children surveyed. As the health system does not need the immunization cards once the vaccination schedule is complete, there is a low retention of cards and hence poor documentation. This could have resulted in over or underestimating the vaccination coverage. This limitation was partially addressed by confirming with the health worker's records and probing about the vaccination history by linking it to the child's milestones.

In conclusion, the findings of our study indicated the persistence of diphtheria Hyderabad. Attack rates of diphtheria were higher in first four circles of the city, where Muslims are in high proportions. Receiving booster doses was key for diphtheria protection. The coverage for primary immunization in three of the seven circles and booster doses in all the circles was low. The coverage of booster doses was low among Muslims.

Based of the findings of our study, we propose following recommendations for the control of diphtheria in Hyderabad. First, there is a need to improve the vaccination coverage for diphtheria boosters at Hyderabad with special emphasis in the four circles with high attack rates. Second, increase the awareness of mothers regarding the importance of booster doses especially among Muslims. This could be taken up intensively through the field health workers. Third, as the attack rates were higher among adolescent children, tetanus toxoid administered to school children at 10 and 15 years of age could be replaced with Td vaccine. Fourth, coverage of boosters could be considered as performance indicators to improve the immunization programme.

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Table 1: Number of cases and attack rates of diphtheria by age and sex, Hyderabad, Andhra Pradesh, India, 2003-2006

Demographic characteristics		Number of cases admitted during 2003-2006	Average population for 2003-2006	Annual attack rate per 100,000
Age	<=1	8	81,050	2
(years)	2-4	116	240,450	12
	5-9	455	415,673	27
	10-14	530	455,426	29
	15-19	431	450,408	24
	20-44	1054	1,583,569	17
	>=45 years	91	632,964	4
Sex	Male	1153	1,983,960	15
	Female	1532	1,875,580	20
Religion	Non-Muslim	811	2270695	9
	Muslim	1874	1588845	29
Total		**2685**	**3,859,540**	**17**

Figure 1: Trend of diphtheria cases at Fever Hospital, Hyderabad, Andhra Pradesh, India, 2003-2006

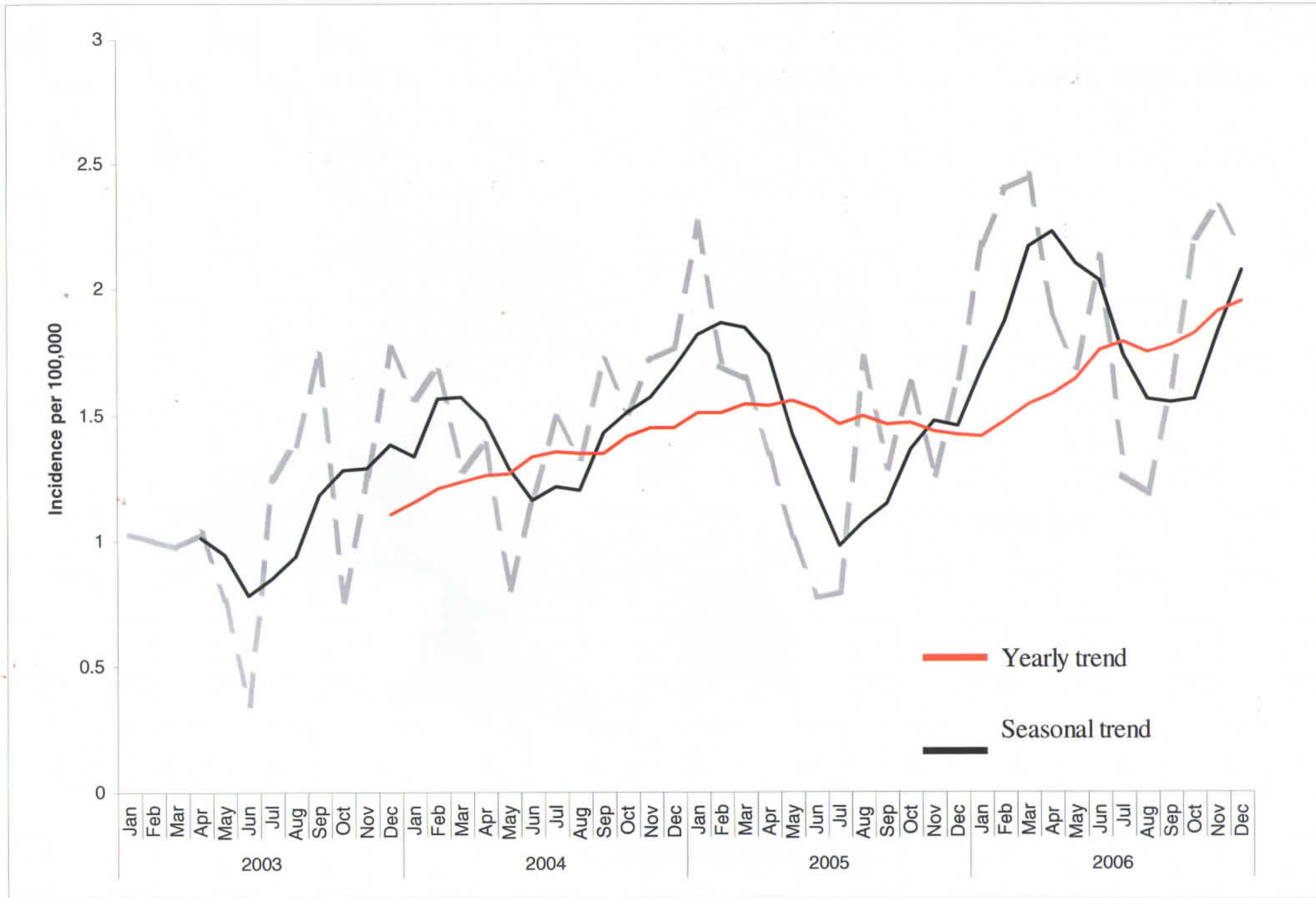

Figure 2: Attack rates of diphtheria in different circles of Hyderabad, Andhra Pradesh, India, 2003-2006

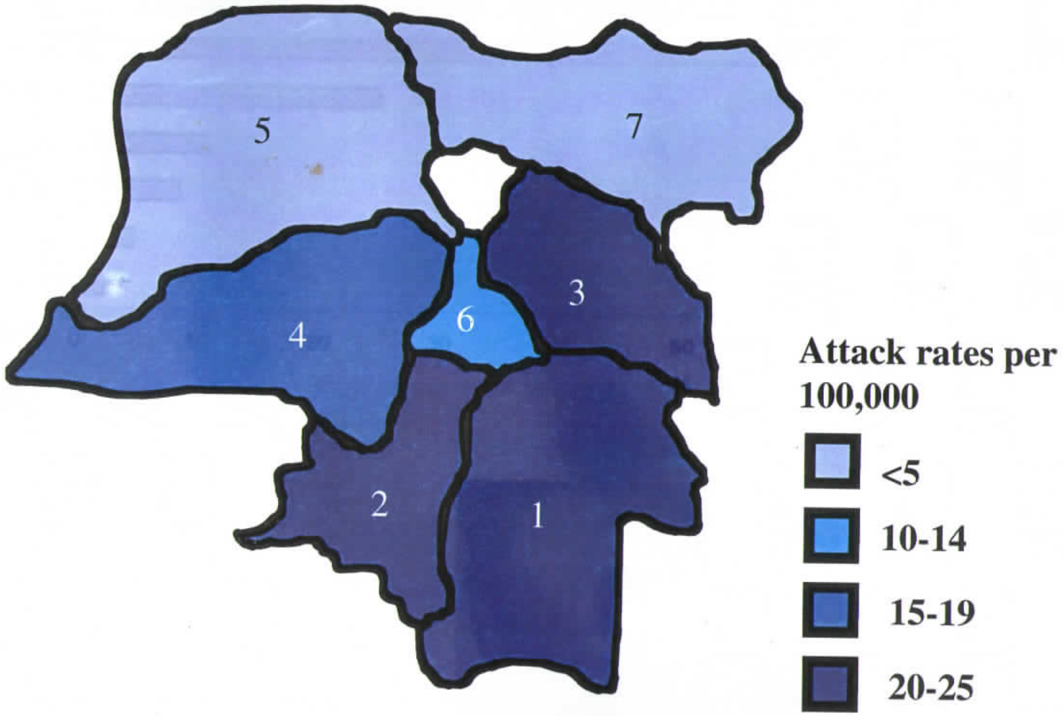

Figure 3: Clinical features of diphtheria cases admitted in Fever Hospital, Hyderabad, Andhra Pradesh, India, 2006

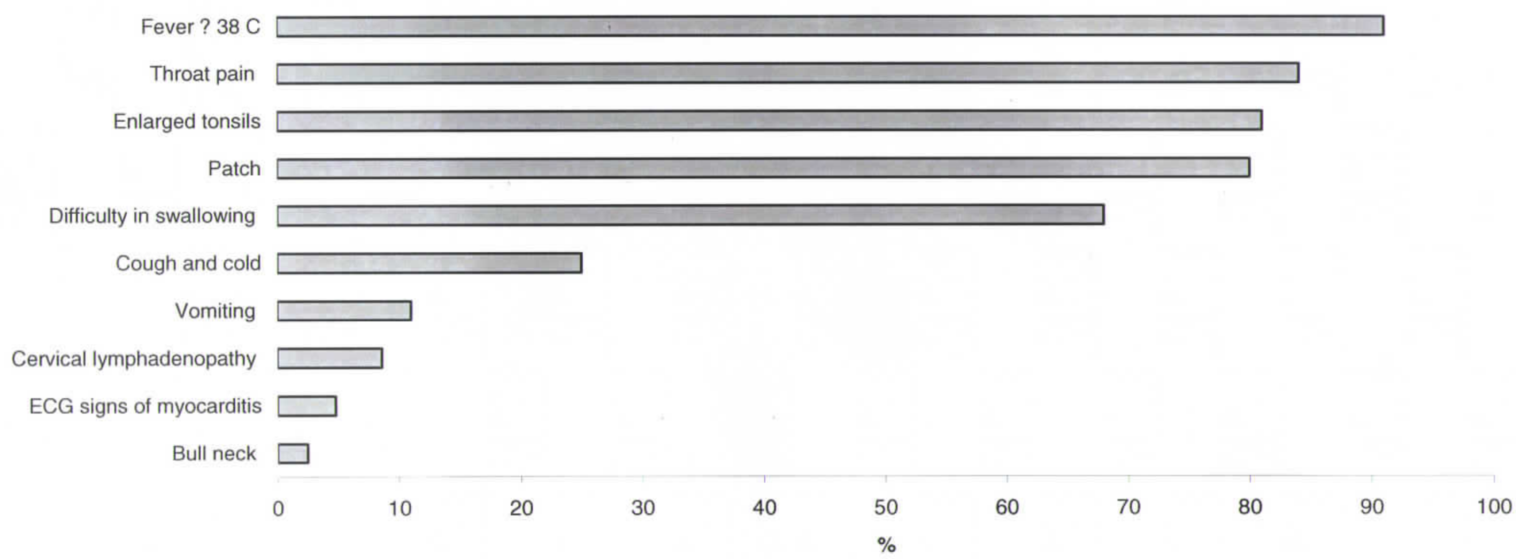

Figure 1: Trend of diphtheria cases at Fever Hospital, Hyderabad, Andhra Pradesh, India, 2003-2006

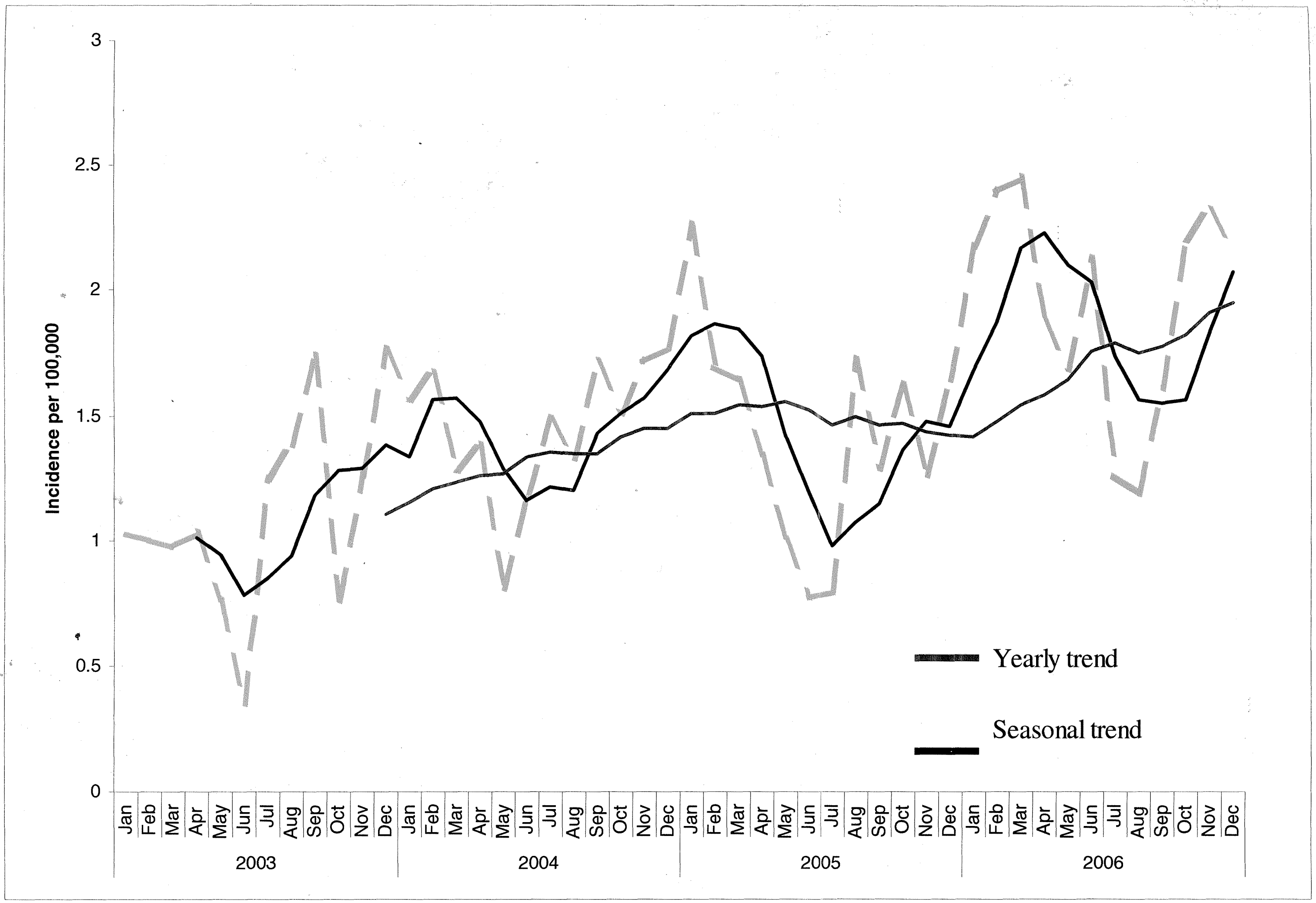

Table 2: Number of doses of diphtheria vaccine received among diphtheria cases and matched controls, stratified with age, Hyderabad, Andhra Pradesh, India, 2006

Number of doses received	0-4 years of age				5 years of age and above					
			Crude vaccine efficacy				Vaccine efficacy			
							Crude		Adjusted[1]	
	Cases	Controls	Estimate	95 CI[2]	Cases	Controls	Estimate	95 CI	Estimate	95 CI
0	6	1	Reference	-	20	12	Reference	-	Reference	-
1	0	1	-	-	7	2	0%	0-69%	0%	0-66%
2	2	0	-	-	6	2	0%	0-74%	0%	0-73%
3	5	7	88%	0-100%	34	26	22%	0-70%	36%	0-77%
4[3]	7	13	90%	0-100%	27	27	40%	0-78%	55%	0-84%
5[4]	0	1	-	-	8	30	84%	48-95%	91%	67-98%

[1] Conditional logistic regression taking into account vaccine doses and religion, family income and literacy status of parents.
[2] Confidence interval
[3] Booster at 18 months of age
[4] Booster at five years of age

Table 3: DPT vaccination coverage among strata of children in the seven circles of Hyderabad, Andhra Pradesh, India 2006.

Circle	Diphtheria vaccine doses in different age groups					
	12-23 months		18-36 months		54-72 months	
	Number surveyed	No. incompletely vaccinated	Number surveyed	No. incompletely vaccinated	Number surveyed	No. incompletely vaccinated
1	94	10	94	46	94	77
2	94	13	94	50	94	74
3	94	9	94	24	94	59
4	94	19	94	39	94	63
5	94	6	94	37	94	71
6	94	8	94	37	94	41
7	94	2	94	29	94	51

Table 4: Immunization status of among Muslim and non-Muslim children

Age group (month)	Muslim		Non-Muslim		Coverage ratio (95% CI)
	No. surveyed	No. completely vaccinated (%)	No. surveyed	No. completely vaccinated (%)	
12-23	223	194 (87%)	435	397 (91.3)	0.95 (0.90-1.1)
18-35	225	122 (54.2)	433	274 (63.3)	0.86 (0.75-0.99)
54-72	217	53 (24.4)	441	182 (41.3)	0.59 (0.5-0.8)

REVIEW OF LITERATURE

1. Microbiology

Diphtheria is an acute infectious disease affecting the upper respiratory tract, and occasionally the skin, caused by the action of diphtheria toxin produced by toxigenic Corynebacterium diphtheriae or by Corynebacterium ulcerans. It is an aerobic, gram positive, non-motile rod showing a club shaped or v-shaped arrangements in normal growth. They undergo snapping movements just after cell division that brings them into characteristic arrangements resembling Chinese letters pattern. It is a fastidious organism, growing slowly even on enriched media like Potassium tellurite agar forming black colonies. A smear stained with Albert's stain shows organisms with metachromatic granules.

Three strains of C.diphtheria are identified gravis, intermedius and mitis named on the basis of the severity of disease they cause in human beings. All strains produce identical toxin and are capable of colonizing the throat. The difference in the virulence between the three strains can be explained by their differing abilities to produce the toxin in rate and quantity and by their differing growth rates. The gravis strain has a generation time of 60 minutes (in vitro), the intermedius has a generation time of 100 minutes and mitis has a generation time of180 minutes. The faster growing organisms produce larger colonies on the growth media.

1.1. Pathogenesis

Diphtheria is a rapidly developing acute febrile illness with local and systemic manifestations. The pathogenesis has two distinct phenomenon, local invasion and toxigenesis.

i) A local lesion develops in the upper respiratory tract causing necrotic injury to the epithelial cells. As a result of this injury plasma leaks into the area and a fibrin network forms interlacing with rapidly growing bacteria. This membranous network covers the site of the local lesion and is referred to as the pseudomembrane. Diphtheria bacilli do not invade tissues below or away from the surface epithelium.

ii) At this site they produce a toxin that is absorbed and disseminated through the lymphatic channels and blood to the susceptible tissues of the body. Degenerative changes in these tissues that include heart muscle, peripheral nerves, adrenals, kidneys, liver and spleen, result in the systemic pathology of the disease.

1.2. Diphtheria toxigenicity

C. diphtheriae produces an exotoxin only after infection by a particular bacterial virus, a bacteriophage. The introduction of a toxigenic strain of C. diphtheriae into a community may initiate an outbreak of diphtheria by transfer of bacteriophage to the non-toxigenic strains carried in the respiratory tracts of inhabitants. Two factors influence the ability of the organism in the production toxin (1) the presence of a lysogenic prophage in the bacterial chromosome and (2) a low extra cellular concentration of iron. The gene for toxin production is present on the chromosome of prophage, but a bacterial repressor protein controls the expression of this gene. The repressor is activated by iron; therefore lysogenic bacteria only under the conditions of iron deficiency produce high yields of toxin.

The faster growing strain causes a depletion of iron stores in the local tissues thereby allowing greater and earlier production of toxin. Also, if the kinetics of toxin production follows the kinetics of bacterial growth, the faster growing organism would achieve effective toxin level faster than the slow growing strains.

When treated with formaldehyde and heat, diphtheria toxin loses its ability to bind to cells and its enzymatic activity, but retains its immunogenicity. This treatment converts diphtheria toxin to a toxoid, which is commonly used to immunize against diphtheria. Two important properties of the diphtheria toxin are utilized to determine the activities of diphtheria antibodies, The first property is the dermonecrotic capacity which is used for the Shick test in humans and to determine neutralization antibody in in vivo systems in animals. The second property is the capacity of diphtheria toxin to block protein synthesis in cultured mammalian cells thus causing cell death. This capacity is utilized to determine diphtheria antibody levels in an in vitro neutralization tests using cells sensitive to diphtheria toxin.

Shick test: This is done to test the immunity of a person against diphtheria. 0.1 ml of the toxin is injected intradermally in to the volar aspect of the forearm of the person being tested. If the person has circulating diphtheria anti toxin at a level of 0.01 to 0.03 IU/ml, the injected toxin will be neutralized and no reaction occurs. A positive reaction signifies lack of antitoxin and is characterized by an inflammation occurring after 24 to 48 hours and persisting for four days or more. A control test is performed on the opposite arm, using toxin inactivated by heating for 60^{o}c for 15 minutes.

1.3. Modes of transmission and Incubation period:

The incubation period of diphtheria ranges from two to five days (1-10 days). Patients with untreated disease may be infectious for up to four weeks. On the other hand, carriers of diphtheria may potentially transmit the infection for a longer period. Transmission of the infection is by droplet and through contact with articles (such as clothing or bed linen) soiled by infected persons. In countries where hygiene is poor, cutaneous diphtheria is the predominant clinical manifestation and source of infection. The normal reservoir of C. ulcerans is cattle. Infections in humans are associated with the consumption of raw dairy products and contact with animals. Person-to-person spread cannot be ruled out, although it is probably uncommon (Bonnet and Begg, 1999).

2. Clinical presentation, complications and treatment:

CDC describes diphtheria as "an upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose". Diphtheria is a rapidly developing, acute, febrile infection that involves both local and systemic pathology. A local lesion develops in the upper respiratory tract and involves necrotic injury to epithelial cells. As a result of this injury, blood plasma leaks into the area and a fibrin network forms that is interlaced with rapidly growing C. diphtheriae cells. This membranous network covers over the site of the local lesion and is referred to as the pseudomembrane. (Todar's textbook of Bacteriology)

The most characteristic feature of diphtheria affecting the upper respiratory tract is a membranous pharyngitis (often referred to as a pseudo-membrane) with fever, enlarged anterior cervical lymph nodes and edema of soft tissue giving a 'bull neck' appearance. The pseudo-membrane may cause respiratory obstruction. Milder infections (without toxin production) resemble streptococcal pharyngitis and the pseudo-membrane may not develop. Carriers may be asymptomatic. Diphtheria toxin affects the myocardium, nervous and adrenal tissues, causing myocarditis and paralysis. The disease is classified based on the site of infection as anterior nasal, pharyngeal and tonsillar, laryngeal, coetaneous, occular and genital.

Most complications of diphtheria, including death, are attributable to effects of the toxin. The severity of the disease and complications are generally related to the extent of local disease. The toxin, when absorbed, affects organs and tissues distant from the site of invasion. The most frequent complications of diphtheria are myocarditis and neuritis. Myocarditis may present as abnormal cardiac rhythms and can occur early in the course of the illness or weeks later, and can lead to heart failure. If myocarditis occurs early, it is often fatal. Neuritis most often affects motor nerves and usually resolves completely. Paralysis of the soft palate is most frequent during the third week of illness. Paralysis of eye muscles, limbs, and diaphragm can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis. Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants. Case fatality rate is 5-10%. Diphtheria is more severe for those under 5 and over 40 years of age.

Treatment of acute cases: Anti diphtheritic serum is administered in doses ranging from 10,000 units to 100,000 units depending upon the severity and site of the disease. Antibiotics, either Benzyl Penicillin (10,000-15,000 units/kg/day) or Erythromycin (50mg/kg/day) are given for a period of fourteen 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.

Treatment of contacts: For close contacts, especially household contacts, a diphtheria booster, appropriate for age, should be given. Contacts should also receive antibiotics—Benzedrine penicillin G (600,000 units for persons younger than 6 years old and l,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). For compliance reasons, if surveillance of contacts cannot be maintained, they should receive benzathine penicillin G. Identified carriers in the community should also receive antibiotics. Maintain close surveillance and begin antitoxin at the first signs of illness (Diphtheria chapter Pink book).

Immunization has played a key role in the control of the diphtheria ever since the vaccine was made available in 1920s. Because of high degree of susceptibility in children, primary immunization with three doses of diphtheria in combination with petusis and tetanus vaccines is universally advocated. The vaccine is administered starting from 2-4 months of age and is given in three doses each one month apart. First booster dose is given one year after the third primary dose and another at school entry. Immunization among adults is not universally done.

3. Immunity

Immunity against diphtheria is antibody-mediated. Because the lethality of diphtheria is almost entirely due to diphtheria toxin, immunity to diphtheria depends primarily on antibody against the toxin. This antibody, called antitoxin, is primarily of the IgG type. Antitoxin is distributed throughout the body and can pass easily through the placenta, providing passive immunity to the newborn during the first few months of life. Diphtheria antitoxin may be induced by diphtheria toxin produced by C. diphtheriae during the disease or the carrier state, or by diphtheria toxoid following immunization. These antibodies are identical and cannot be distinguished by any existing techniques.

4. Epidemiology

4. 1. Diphtheria in pre-vaccine era

In the pre-vaccine era, when circulation of C. diphtheriae organisms was frequent and the prevalence of diphtheria cases was high, natural immunity acquired by apparent infection or inapparent infection was the only mechanism of acquiring immunity. Diphtheria was primarily a disease of children. Most newborn infants had antibody acquired passively from their mothers; this passive antibody waned between 6 and 12 months of age. Then immunity rose rapidly in early childhood, reflecting increasing exposure to diphtheria organisms. By the age of 15 to 20 years, nearly all persons had acquired natural immunity to diphtheria. The process of acquiring natural immunity was rapid, in some countries more than 80% of children were immune by 10 years of age. This pattern was observed in industrialized as well as developing countries before the diphtheria immunization was introduced.

When diphtheria was a common disease, it most commonly affected children. About 40% of the cases were under the age of five years and some 70% were under the age of 15 years. This classical pattern was seen in many countries (Euro surveil 1997; 2(8): 60-63) between 1907 to 1937. In the pre vaccine era, exposure to toxigenic strains of diphtheria organisms was common, and this provided natural boosts to the development and maintenance of immunity against diphtheria. Children were susceptible and most adults remained immune to the disease. Historical data however shows that the shift in the age has started even before the mass immunization programmes were introduced in many countries.

4.2. Diphtheria vaccine

In 1909, Theobald Smith, in the U.S. demonstrated that diphtheria toxin neutralized by anti-toxin (forming a toxin-anti-toxin complex (TAT) remained immunogenic and eliminated the local reactions seen in the heat modified toxin. Beginning from 1910 TAT was used for active immunization against diphtheria. TAT had two undesirable side effects (1) it was highly toxic and the quantity injected could result in fatal toxemia unless the toxin injected is not fully neutralized by antitoxin (2) it was derived from Horse's serum and the components tended to be allergenic and sensitize individuals to serum.

In 1929, Ramon demonstrated the conversion of diphtheria toxin to its non-toxic but antigenic equivalent (toxoid) by using formalin. The vaccine is always given in combination as DPT or DT or Td or DaPT.(Todar's text book of bacteriology)

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%. Diphtheria toxoid has been estimated to have a clinical efficacy of 97%.(Diphtheria chapter Pink book)

4.3 Diphtheria in post-vaccine era: Developed countries

The incidence of diphtheria in the developed nations declined following effective immunization programs since the 1920's(1). During the 1940s-1950s, the introduction of universal childhood immunization with diphtheria toxoid nearly eliminated diphtheria in most industrialized countries. However, a resurgence of the disease has been observed in these countries, largely attributed to waning vaccine immunity in adults and importation of cases from the endemic developing world (2).

In the pre-vaccine era, diphtheria was a major cause of childhood illness and death worldwide. After the introduction of diphtheria toxoid vaccine, a decline in diphtheria cases was seen where the vaccine was used.

4.4 Diphtheria in post-vaccine era- Developing countries:

Diphtheria still remains endemic with increase in the fulminant complications and mortality in the last two decades, especially in children above 5 years (3). Factors like inadequate vaccine coverage (4), poor socio-economic standards, overcrowding, delayed reporting to hospital, non-availability and delay in administration of antitoxin further contribute to the high mortality.

4.5 Diphtheria epidemics:

Recent epidemics of the Newly formed Independent states (USSR) during 1990 to 1995 during which 157,000 cases and 5,000 deaths were reported have been largely attributed to

a) Decreased immunization coverage among infants and children
b) Waning immunity to diphtheria in adults
c) Population migrations
d) Irregular supply of vaccines
e) Late recognition of the epidemic

Diphtheria outbreak in various provinces of Thailand between 1990-1999 resulted in 425 case and 83(case fatality:19.5%). The reported coverage in all the provinces was more than 90%.76.3% of the total case were under ten years of age. The increase in the attack rates in the 90s was largely attributed to sub-optimal immunization rates among minorities and economically disadvantaged populations.

Clinical features including Treatment: The Kyrgyz Republic experienced a widespread resurgence of diphtheria during 1994-1998.To describe the clinical characteristics and management of diphtheria patients hospitalized in 1995, a retrospective chart review was conducted. Physician-diagnosed cases of diphtheria were classified according to the system recommended by the World Health Organization and UNICEF. Among hospitalized with respiratory diphtheria, 24% were carriers, 28% had tonsillar forms, 12% had combined types or delayed diagnosis, and 30% had severe forms of diphtheria. Myocarditis occurred among 22% patients, 5% had neuritis and 3% patients died. Respiratory diphtheria remains a potentially fatal disease, commonly presenting with a typical membranous pharyngitis. Early diagnosis and treatment of cases with diphtheria antitoxin and antibiotics are the cornerstones of effective treatment.

The antibiotics of choice for treatment of patients with diphtheria are penicillin or erythromycin, and they should be administered for 14 days. The dose of Diphtheria antitoxin is based on the site and severity of the disease ranging from 10,000 to 100,000 units. Because clinical diphtheria does not necessarily confer natural immunity, patients with diphtheria should be vaccinated before hospital discharge.

4.6 Risk factors:

The large-scale resurgence of diphtheria in the former Soviet Union offered a unique opportunity to evaluate risk factors for the transmission of respiratory diphtheria; therefore, a prospective case-control study was done in the republic of Georgia. In the multivariate analyses, the following risk factors were found to be significant: lack of vaccination, household exposure to diphtheria, exposure to skin lesions, history of eczema, fever with myalgia prior to illness, having tonsils, sharing a bed, sharing cups and glasses, and taking a bath less than once a week . These findings emphasize primary prevention through immunizations, secondary prevention following exposure to diphtheria (and to suspicious skin lesions),and adherence to strict standards of personal hygiene.

4.7.Vaccine efficacy

A case-control study in Ukraine provided the first data on the field effectiveness of Russian produced vaccine during the 1990 diphtheria resurgence in the former Soviet Union. The effectiveness of three doses of diphtheria vaccine was 98.2% (95% confidence interval: 90.3-99.9), increasing to 99.7% (95% CI: 97.2-100.0) with four doses and to 99.9% (95% CI: 89.7-100.0) with five or more doses.

4.8.Control strategies

In epidemic situations: A plan for coordinated action to control epidemic diphtheria in the countries of the former USSR was elaborated in 1995 by WHO and UNICEF in close collaboration with the Center for Disease Control and Prevention (CDC), the IFRC, USAID, Basic Support for Institutionalizing Child Survival, and the Program for Appropriate Technology in Health; this plan was approved by representatives of the NIS and Baltic States.

The three main components of the strategy follow:

1. Initiate mass immunization as rapidly as possible of all age groups in the population with at least one dose of diphtheria toxoid (later modified to include two additional doses for selected age groups, e.g., persons 30-50 years of age).
2. Provide early detection and proper management of diphtheria cases.
3. Provide early identification and proper management of close contacts of diphtheria cases.

In non epidemic situations:

1.The achievement of high immunization coverage (>90% of the population) with a primary series of three doses of DTP vaccine is of utmost importance.

2.The use of a fourth dose of DTP vaccine in preschool-age children is recommended in countries that have achieved high coverage with the primary series. Usually, it is given between 12 and 36 months of age. The immunization coverage with this dose should also exceed 90%.

3.Immunization of school-aged children is recommended. For children immunized in infancy with DTP or DT (diphtheria-tetanus toxoids) vaccines, a booster dose is recommended when they enter and, preferably, when they leave school. In children !7 years of age, DT vaccine should be used, and in older children, Td vaccine is indicated.

4.Countries that have successfully controlled diphtheria through infant and childhood immunization programs should maintain immunity against diphtheria in adults by the use of Td vaccine (or d vaccine, an adult-type monovalent diphtheria toxoid for persons with a high immunity against tetanus). The choice of strategies depends on local conditions; Td vaccine can be given as periodic booster doses every 10–20 years, or the selected strategy can be age-specific for ages at which people are in contact with health care providers.

5.The strategy that proved effective in the NIS epidemic was mass immunization of the entire population with at least one dose of diphtheria toxoid-containing vaccine, regardless of the previous immunization history, and two additional doses for specific age groups with low-level immunity (e.g., 30- to 50-year-old adults).

6.Special efforts should be undertaken to monitor diphtheria immunity in different groups by conducting age-specific serologic studies. In countries where diphtheria is successfully controlled and where there are no diphtheria cases, results of serologic testing are important for assessing the risk of diphtheria. In countries where diphtheria cases are still being reported, changes in age distribution of cases and trends in diphtheria incidence are useful factors for assessing the risk.