A Case–control Study of Diphtheria in the High Incidence City of Hyderabad, India

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Background: India accounts for approximately 72% of reported diphtheria cases globally, the majority of which occur in the state of Andhra Pradesh. The aim of this study is to better understand lack of knowledge on diphtheria vaccination and to determine factors associated with diphtheria and low knowledge and negative attitudes.

Methods: We performed a 1:1 case–control study of hospitalized diphtheria cases in Hyderabad. Eligible case patients were 10 years of age or older, resided within the city of Hyderabad and were diagnosed with diphtheria per the case definition. Patients admitted to the hospital for nonrespiratory communicable diseases and residing in the same geographic region as that of cases were eligible for enrolment as controls

Results: There were no statistical differences in disease outcome by gender, education, economic status and mean room per person sleeping in the house in case and control subjects. Not having heard of diphtheria (adjusted odds ratio: 3.56; 95% confidence intervals: 1.58–8.04] and not believing that vaccines can prevent people from getting diseases (adjusted odds ratio: 3.99; 95% confidence intervals: 1.18–13.45) remained significantly associated with diphtheria on multivariate analysis.

Conclusion: To reduce the burden of diphtheria in India, further efforts to educate the public about diphtheria should be considered.

Key Words: diphtheria, immunization, India, knowledge

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Diphtheria is a highly contagious and potentially life threatening upper respiratory tract bacterial disease caused by *Corynebacterium diphtheriae*. The World Health Organization (WHO) recommends 3 doses of Diphtheria Pertussis and Tetanus vaccine starting at 6 weeks of age with additional boosters at 18 months and 5 years of age. After 3 doses of primary vaccine, protective levels of antitoxin develop in 94–100% of the children. However, without booster doses, over time toxoid-induced antibody drops below protective level.[1]

In 1985, India introduced the Universal Immunization Programme (UIP), with the goal of reaching at least 85% coverage in infants for many vaccine-preventable communicable diseases, including diphtheria, following WHO's recommended vaccine schedule.[2] However, evaluations of UIP coverage have shown a significant shortfall in reaching this goal. Estimates of coverage have ranged from 29% to 61%, depending on area of residency.[2] Either re-emergence or persistence of diphtheria has been reported from several Indian states.[3] India is a critical geographic location for the study of diphtheria because it accounts for approximately 72% of reported cases globally.[4] However, 70% of India's cases are reported from the state of Andhra Pradesh of which 16% are derived from the city of Hyderabad.[5]

The data on vaccine-preventable diseases provided by the Government of India to WHO during 1980–2008 indicate persistence of diphtheria without much decline over the last 25 years.[6] During these years, there has been a shift in the epidemiology of diphtheria in India. First, the disease, which was common among children younger than 5 years,[7] is now affecting many older children (5–19 years) and adults. Second, in certain states, the disease is relatively common among females and Muslims.[3,8] However, the majority of cases reported were from children who were either unimmunized or partially immunized against diphtheria. Low coverage of primary immunization, as well as boosters, has likely contributed to these epidemiological changes.[4]

A study of diphtheria in Hyderabad during 2003–2006 revealed the highest incidence among children aged 5–19 years, women and Muslims, with an average attack rate of 17 per 100,000.[3] In another recent study, less than 80% of children in 4 out of 7 circles of Hyderabad were receiving primary diphtheria vaccinations or boosters, and a serosurvey revealed that only 56% of children aged 7–17 years had protective immunity.[9] Primary reasons reported for parents/caretakers failing to vaccinate their children were inadequate knowledge about vaccination (48%), facing obstacles to get vaccinated (32%) and/or lacking motivation (20%).[9] To better understand lack of diphtheria vaccination knowledge and to determine factors associated with diphtheria and low knowledge and negative attitudes in this high incidence city, we performed a case–control study of hospitalized diphtheria cases in Hyderabad. We hypothesized that younger age, female gender, Muslim religion and not having heard of diphtheria would be associated with being a case.

METHODS

Study Setting

Subjects were recruited from July through September 2013 at the Ronald Ross Institute of Tropical and Communicable Diseases, also known as the Fever Hospital, in Hyderabad, India. This hospital serves as a referral and primary care hospital for infectious diseases, such as diphtheria, diarrhea, measles, mumps, cholera and hepatitis. This is a public health facility with 150 in-patient beds and a separate ward for infectious diseases.

Study Population

Potential participants for the study were identified after admission to the hospital. Adult patients and parents/legal guardians of children aged 10–17 years or older with clinical diphtheria diagnosed by a physician were asked to participate in the study. Patients admitted to the hospital for nonrespiratory communicable diseases and residing in the same geographic region as that of cases were eligible for enrolment as controls.

Data Collection

Data were collected using a close-ended questionnaire administered to patients, or in the case of minors, administered to

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an accompanying adult (typically the patient's mother or father). The questionnaire asked about demographic and socioeconomic information; knowledge of diphtheria with respect to transmission, symptoms severity and on diphtheria vaccination booster doses; attitudes toward vaccination and primary sources of health information. Knowledge of diphtheria was assessed by asking questions on whether the cases or controls had heard of diphtheria and knew that diphtheria spreads from one person to another, diphtheria spreads through droplets, diphtheria causes a severe sore throat and diphtheria can lead to death.

The questionnaire was performed in Telugu or English, according to the indicated preference of the participant, by a social worker trained and experienced in research data collection and fluent in the respective languages. The questionnaire was administered to the cases and controls after recovery from the acute phase of infection. All study instruments were developed in English, translated into Telugu, then back-translated to ensure fidelity.

Study Design

A case–control study, with a 1:1 case–control ratio was performed. Eligible case patients were 10 years of age or older, resided within the city of Hyderabad and diagnosed with diphtheria, as determined by the trained senior physician. Diphtheria patients records were reviewed to confirm that cases met the WHO clinical description; illness characterized by laryngitis, pharyngitis or tonsillitis and an adherent membrane of the tonsils, pharynx and/or nose. Controls were selected from the patients visiting the hospital with nonrespiratory symptoms, residing in Hyderabad and had a clinic visit on the same day as the case. Controls were matched to cases by age range: 10–14, 15–19, 20–29 and >30 years.

Information on risk factors that might affect knowledge concerning immunization (eg, occupation and education status of the caretaker and the subject) were collected. To assess the economic status of the case and controls, the questionnaire also assessed if they were in possession of a white ration card (which is issued to the below poverty line citizens in India).

Sample Size

The sample size was determined, considering a 5% (alpha) probability at which results would be deemed statistically significant, and 90% power assuming 70% proportion of controls with exposure (has knowledge on vaccination) and 40% proportion of cases with exposure, 63 controls and 63 cases was the estimated sample size for this 1:1 case–control study.

Data Analysis

Pearson χ^2 tests were used to examine the significance of associations of exposure variables and diphtheria status (case or control). *P* values were considered significant at a level of <0.05. Means and medians were calculated to summarize continuous variables.

Continuous variables were dichotomized. Median age was calculated, and age less than or equal to the median was compared with above. Education of both the cases/controls and the caretaker was examined based on lowest educational status (never attended school and completed elementary schooling) versus any higher education (attended or completed secondary school or any higher education, which includes professional training school, college and university). Occupation of cases and caretaker compared no job with others (student, teacher, office worker, industry worker, transportation, household servant and daily wage earner). Fewer than or equal to 1.5 persons per room was compared with versus.

Estimates of odds ratios and accompanying 95% confidence intervals (CIs) were calculated for risk factors and their combinations. Adjusted odds ratios for combinations of risk factors were derived from their respective model coefficients in a multivariate logistic model. All the independent variables that were significantly associated ($P < 0.05$) were introduced into the logistic regression with having diphtheria as an outcome variable. Data entry and statistical analyses were carried out using SPSS version 16 v. (SPSS Inc., Chicago, IL). All statistical tests of hypotheses are 2 sided.

Protection of the Human Subjects

We explained the objectives, methods, benefits and risk of our study to the participants and obtained written informed consent. We used unique identification numbers for each participant to maintain confidentiality. Institutional review board approval for the study was provided by the University of Illinois at Chicago, US and the Medi-citi Institute of Medical Sciences in India.

RESULTS

Between June and September 2013, 63 cases and 63 controls were interviewed. The median age of the study population was 21 years (range, 10–45 years, including 31 aged 10–19 years, 19 aged 20–29 years, 12 aged 30–39 years and 1 aged ≥40 years). The occupation of cases and controls of included student (49%), teacher (0.7%), office worker (3.9%), industry worker (0.7%), transportation worker (4.7%), daily wage (7.1%), odd jobs (18.2%) and no job (15.0%). The occupation of caretakers included teacher (2.4%), office worker (6.3%), industry worker (1.6%), transportation worker (2.4%), daily wage (14.3%), petty business (36.5%) and no job (23.0%). About 15% and 20% of cases and controls have never attended school and had completed elementary school education and 37% had completed higher education. Predominantly, 48% of the caretakers never attended school, 27% completed secondary education and 18% had completed higher education.

There was no statistical difference in disease outcome by gender, religion (Muslim and non-Muslim), education of both the primary caretaker and the case or control, economic status as indicated by having a white ration card and number of persons per room sleeping in the house of a case and control (Table 1). Cases and controls did not differ in sociodemographic and economic characteristics (Table 1). Control subjects had significantly higher knowledge about diphtheria infection and diphtheria booster doses and had a positive attitude toward considering taking vaccines (Table 2). Approximately, 1 in 3 controls were aware that Hyderabad had more cases of diphtheria than elsewhere compared with only about 1 in 13 cases. Although not significant, cases had greater awareness that diphtheria causes a severe sore throat (as expected, 100% were aware compared with 83.9% for controls).

After inclusion in the regression, analysis model of independent variables significantly associated with the outcome in univariate analysis, not having heard of diphtheria and not believing that vaccines can prevent people from getting diseases remained significantly associated with diphtheria (Table 3). Both cases and controls (70%) responded that the source of information regarding vaccines was primarily from the physicians.

DISCUSSION

The WHO recommends diphtheria vaccination for all children. India's UIP has attempted to meet that goal. However, this case–control study reveals that increased public education about diphtheria and the value of immunization may need increased attention as an adjunct to universal vaccine availability in the high incidence city of Hyderabad, India.

TABLE 1. Frequency of Sociodemographic and Economic Characteristics of Diphtheria Patients Compared with Control Subjects

Characteristics		Case (N = 63), n (%)	Control (N = 63), n (%)	Odds Ratio	95% CI	*P*
Median age (21 yrs)	≤21 yr	38 (60.3)	38 (60.3)	1	0.52–2.16	1
Gender	Male	33 (52.4)	33 (52.4)	1	0.49–2.01	1
Religion	Muslim	32 (50.8)	22 (34.9)	1.924	0.94–3.93	0.071
	Hindu	31 (49.2)	41 (65.1)			
Education	Never attended school	11 (17.5)	8 (12.7)	1.454	0.54–3.90	0.462
Education of caretaker	Never attended school	29 (46)	28 (44.4)	1.066	0.52–2.15	0.861
Occupation	No job	08 (12.7)	18 (28.6)	1	0.48–2.05	0.855
Occupation of caretaker	No job	10 (15.9)	17 (27)	0.511	0.21–1.20	0.131
Eligible for white ration card	Yes	33 (52.4)	39 (61.9)	0.677	0.33–1.37	0.283
Mean persons sleeping in house	≤5 persons	42 (66.7)	47 (74.6)	0.681	0.31–1.47	0.331
Mean rooms in house	≤2	39 (61.9)	41 (65.1)	0.872	0.42–1.80	0.710

TABLE 2. Frequency of Knowledge and Attitude Toward Spread of Diphtheria and Booster Doses of Vaccine Among Diphtheria Patients Compared with Control Subjects

Characteristics		Case (N = 63), n (%)	Control (N = 63), n (%)	Odds Ratio	95% CI	*P*
Knowledge of diphtheria						
Heard of diphtheria	Yes	13 (20.6)	31 (49.2)	3.726	1.69–8.17	0.001
Diphtheria spreads from one person to another*	Yes	9 (69.2)	20 (64.5)	1.238	0.309–4.962	0.763
Diphtheria spreads through droplets*	Yes	8 (61.5)	20 (64.5)	0.881	0.231–3.353	0.851
Diphtheria causes a severe sore throat*	Yes	13 (100)	26 (83.9)	3.667		0.124
Diphtheria can lead to death*	Yes	10 (76.9)	19 (61.3)	2.105	0.480–9.237	0.318
Hyderabad has more cases of diphtheria*	Yes	1 (7.7)	12 (38.7)	0.132	0.015–1.149	0.040
Knowledge about booster doses of diphtheria						
Additional (booster) doses of diphtheria vaccine	Yes	10 (15.9)	29 (46.0)	.221	0.096–0.511	0.000
Booster doses are needed to stay protected	Yes	10 (15.9)	30 (47.6)	.208	0.090–0.479	0.000
How many booster doses are recommended	2	1 (1.6)	9 (14.3)	.097	0.012–0.789	0.008
What age a child should gets the final booster dose	5 yr	3 (4.8)	19 (30.2)	.116	0.032–0.416	0.000
Attitude toward vaccines						
Vaccines can prevent people from getting diseases	Yes	48 (76.2)	59 (93.7)	4.609	1.44–14.8	0.006
Vaccines are safe	Agree	4 (6.3)	3 (4.8)	1.356	0.291–6.322	0.697
Fear or worries about vaccines	Yes	9 (14.3)	5 (7.9)	1.933	0.610–6.132	0.257

*Comparison subgroups - (cases, 13; controls, 31). These are subset of responses to Heard of diphtheria.

TABLE 3. Association of Select Significant Risk Factors After Multivariate Analysis

Characteristics		Cases (n = 63), N (%)	Controls (n = 63), N (%)	Adjusted Odds Ratio	95% CI	*P*
Heard of diphtheria	Yes	13 (20.6)	31 (49.2)	3.561	1.58–8.04	0.002
Vaccines can prevent people from getting diseases	Yes	48 (76.2)	59 (93.7)	3.990	1.18–13.45	0.026

The population distribution of religious groups in Hyderabad, according to the 2011 census, is approximately 55% Hindu, 41% Muslim and 4% other (eg, Christian and Sikh).[10] A study of immunization coverage for basic UIP vaccines (eg, diphtheria, pertussis, measles and polio) among children of HIV-infected people in Kolkata reported that Muslims were more than 3 times significantly more likely to be incompletely immunized.[11] Given the high incidence of diphtheria in Hyderabad, where diphtheria vaccine coverage is lowest among Muslim children,[5] more attention is needed to target educational efforts to reduce the burden of disease. A United Nations International Children's Emergency Fund (UNICEF) report highlighted that failure to sufficiently vaccinate children in the Muslim population may be due to distrust in the government, low socioeconomic status and education.[12] Although our results did not show a significant association between socioeconomic status and diphtheria, our study hospital generally admits persons of lower socioeconomic status limiting our ability to examine this issue. Also, we did not ask about distrust. Future studies or educational efforts should consider potential distrust during any outreach efforts.

Lack of knowledge of a disease and the value of immunization are fundamental issues that should not be overlooked or underemphasized in disease prevention efforts. Similar to our findings, lack of knowledge has been reported as a primary hindrance to complete immunization in Hyderabad.[9] Other studies have found that vaccine coverage is lower among children whose primary caretakers have lower than a secondary education and particularly

among those who are illiterate.[13,14] Our results, however, did not show an association between the education of primary caretakers and having diphtheria. Primary health physicians are the first point of contact to provide and seek information regarding the vaccine availability and schedule in most Indian societies. Hence, disseminating information by the physicians regarding immunization could be an efficient strategy.

A potential limitation of our study is the lack of microbial culture confirmation. However, all cases met the WHO case definition and were ill enough to warrant hospitalization. In addition, a study of this patient population conducted from January 2008 through December 2012 demonstrated that *Corynebacterium diphtheria* was often isolated from nonimmunized patients [1731 of 2952 (58%)].[15] Therefore, we suspect that many of our patients are also true cases. Our data remain important despite this limitation because they help to quantify knowledge and attitudes regarding immunization among vulnerable persons in this high incidence city. In addition, reporting bias could have occurred if caretakers inaccurately reported lack of knowledge as a way of avoiding blame for their children acquiring the disease. Inaccurate reporting of other factors should also be considered, including average monthly income, which is commonly underreported. Finally, recall accuracy may have been lower in older persons, such as for knowledge about booster doses.

We recommend that health education can be imparted to promote disease and immunization awareness. Future immunization campaigns should consider targeted community education, partnering with community leaders who may be trusted as a source of health information. The emphasis should be on the usefulness of vaccination, misconceptions related to vaccination and the availability of the same, especially among high incidence subpopulations. Importance of maintaining vaccine cards and the accessing all the booster doses should be part of the health promotion activities by the trusted primary health physicians. Because literacy may be a complicating factor in low literacy areas, both literary and nonliterary materials should be developed. Combining immunization with health education programs could be a more potent way to boost community immunization rates and reduce the diphtheria burden in Hyderabad and possibly throughout low immunization rate areas elsewhere in India.

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