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Review Article

Epidemiology of Diphtheria in India, 1996–2016: Implications for Prevention and Control

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Abstract. Diphtheria is an acute disease caused by exotoxin-producing *Corynebacterium diphtheriae*. Globally, diphtheria has been showing a declining trend due to effective childhood vaccination programs. A substantial proportion of global burden of diphtheria is contributed by India. Hospital-based surveillance studies as well as diphtheria outbreaks published in last 20 years (1996–2016) indicate that diphtheria cases are frequent among school-going children and adolescents. In some Indian states, Muslim children are affected more. As per the national level health surveys, coverage of three doses of diphtheria vaccine was 80% during 2015–2016. Information about coverage of diphtheria boosters is not routinely collected through these surveys, but is expected to be low. Few studies also indicate low diphtheria immunity among school-going children and adults. The strategies for prevention of diphtheria need to focus on improving coverage of primary and booster doses of diphtheria vaccines administered as a part of Universal Immunization Program as well as introducing diphtheria vaccine for school-going children.

INTRODUCTION

Diphtheria is an acute infectious disease of upper respiratory system, caused by toxigenic strains of *Corynebacterium diphtheriae*. Diphtheria was a leading cause of childhood morbidity and mortality in the prevaccination era.[1] The incidence of diphtheria has gradually declined in developed as well as developing countries owing to effective immunization programs.[2] However, there has been a reemergence of diphtheria in many countries, largely attributed to low vaccine coverage and waning vaccine immunity in adults.[3] India accounts for a substantial proportion of global burden of diphtheria and many outbreaks have been reported in recent years.

The published literature on diphtheria since 1996 from India was reviewed to describe its epidemiology and suggest recommendations for its control in India.

METHODS

The following sources of data about diphtheria disease burden, outbreaks, immunity, and vaccine coverage were used: 1) World Health Organization (WHO) estimates of disease burden: this database contains the information about the number of diphtheria cases reported by every Member State to WHO/UNICEF using the Joint Reporting form.[4] 2) Annual reports of the Central Bureau of Health Intelligence (CBHI),[5] Government of India, on national health profile: this report contains the information about selected health conditions reported by the Indian States to the CBHI. 3) Medline database: the Medline database was searched for articles published between 1996 and September 2016 for studies on the burden of diphtheria in India as well as immunity against diphtheria. Internet search was also carried out to search for articles in nonindexed journals. The search consisted of terms related to diphtheria ("diphtheria," or "*Corynybacterium diphtheriae*") combined with terms for Indian geography (including a list of state names). Titles and abstracts of articles were read to identify potentially relevant articles. Studies were considered eligible for further examination in full text if they reported number of cases, mortality due to diphtheria, or immune status against diphtheria. Information about age, gender, and vaccination status of cases, and place of study/outbreak was abstracted. Median age of cases was calculated based on the age distribution of the cases. 4) National level surveys about diphtheria vaccine coverage: information about the coverage of diphtheria vaccines was abstracted from the reports of the National Family Health Surveys (NFHSs) conducted during 1998–1999 (NFHS-2), 2006–2007 (NFHS-3) and 2015–2016 (NFHS-4); the District Level Household surveys (DLHSs), conducted during 1998–1999 (DLHS-1), 2002–2004 (DLHS-2), and 2007–2008 (DLHS-3); the Coverage Evaluation Survey, conducted during 2009–2010 and Rapid Survey on Children (RSOC) conducted during 2013–2014.[6–13]

RESULTS

Trend of diphtheria and geographic distribution. Globally, the number of diphtheria cases has been showing a declining trend since 1980, except for a small peak during mid-1990s, corresponding to re-emergence of diphtheria in former Union of Soviet Socialist Republics (Figure 1).

The number of cases reported to WHO has declined from nearly 100,000 cases in 1980 to 2,500 cases in 2015. A similar decline was also observed in India; however, India accounted for majority of diphtheria cases reported globally. During 2001–2015, nearly half of the diphtheria cases reported globally were from India.

As per the CBHI data, during 2005–2014, India reported 41,672 cases (average: 4,167 per year) with 897 deaths (case fatality ratio: 2.2%). Ten Indian states (Andhra Pradesh, Assam, Delhi, Gujarat, Haryana, Karnataka, Nagaland, Maharashtra, Rajasthan, and West Bengal) accounted for 84% cases reported (Figure 2).

Age distribution of diphtheria cases. Pubmed and internet search yielded 33 studies on diphtheria published during 1996–2016 (till September) (Table 1).[14–46] This included 26 studies about hospital/laboratory based surveillance and seven investigations of diphtheria outbreaks. Thirty one studies for which full-text copies were retrieved were included in the analysis (Table 1). Of these, the age distribution of diphtheria cases was available in 24 (17 surveillance

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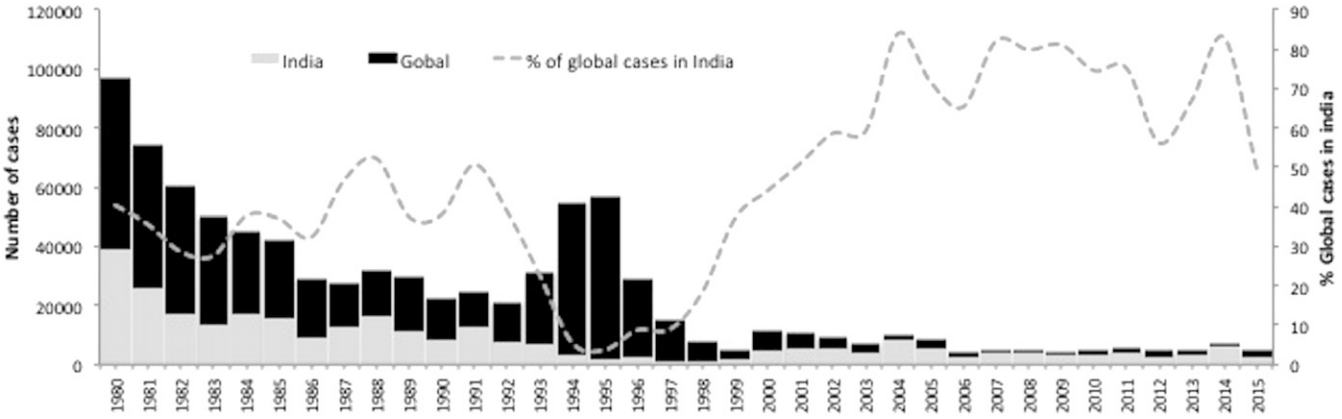

FIGURE 1. Trend of diphtheria cases reported globally and from India, 1989–2015.

studies, seven outbreaks), whereas two studies provided the median/mean age of diphtheria cases.

Only two studies provided overall and age- and sex-specific attack rates—the overall incidence of diphtheria in Delhi during 1997 was 0.65 per 100,000 with rates ranging between 4.73, 2.93, 1.54, and 0.09 per 100,000 in the age group of < 1, 1–4, 5–9, and ≥ 10 year age groups, respectively.[14] The overall incidence in Hyderabad, Andhra Pradesh, during 2003–2006 was 11 per 100,000 with higher attack rates among individuals aged 5–9 (27 per 100,000), 10–14 (29 per 100,000), and 10–19 (24 per 100,000) years, as compared with those aged < 5 years (9.6 per 100,000) or older than 20 years (12.9 per 100,000).[39] Another study by Iyer and others reported that 1,461 cases of diphtheria were reported from the State of Gujarat during 2005–2011 with an average incidence of 0.35 cases per 100,000 population per year. The diphtheria rates showed a decline during this period.[22]

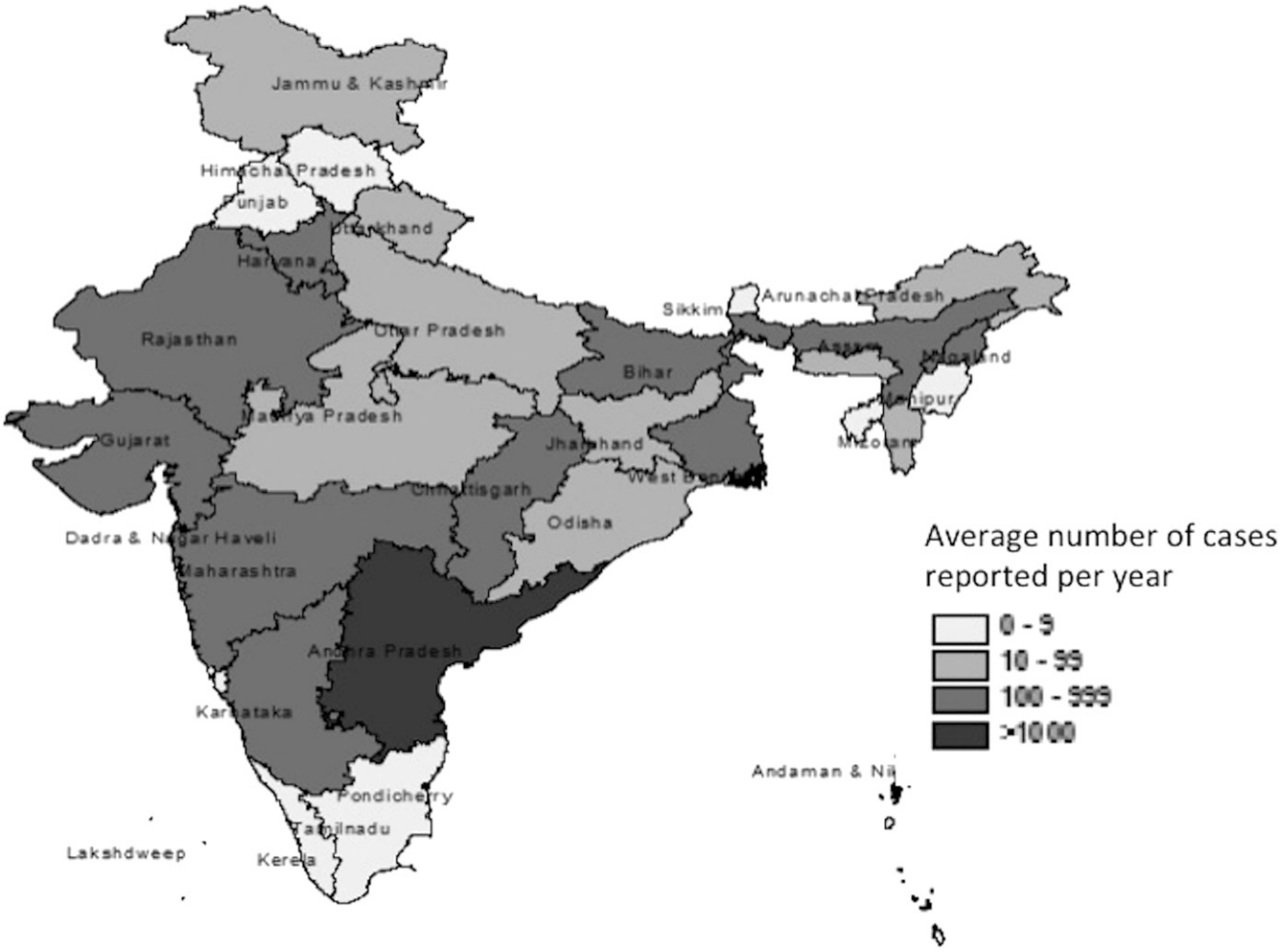

FIGURE 2. Average number of diphtheria cases by different states, India, 2005–2014.

TABLE 1

Studies on diphtheria included in the review

State	Reference	Author	Year of study	District	Setting	*N*	Age groups (year)				Median age	% Males	PCV
Delhi							0–4	5–9	> 9				
	14	Singh J	1997	Delhi	H	143	93	38	12		3.1	62.9	10.5
	15	Sharma N	1998–2004	Delhi	H	493	241	219	33		5.1	61.4	3
							≤ 5	6–9					
	16	Singhal	1999	Delhi	H	10	6	4			5	70	10
	17	Lodha*	1999	Delhi	H	4	3–8 y				NA	25%	50
							≤ 5	> 5					
	18	Kanwal†	2008–2010	Delhi	H	48	29	19			4.3	75	0
							≤ 5	6–10	> 10				
	19	Bhagat	2012–2014	Delhi	H	941	550	251	142		4.4	NA	NA
Gujarat							≤ 5	6–10	> 10				
	20	Patel	1999–2002	Rajkot	H	126	78	43	5		4	51.6	3.7
							1–4	5–9	10–19				
	21	Talsania	2007	Banaskata	O	60	7	25	28		7.8	61.7	NA
	22	Iyer‡	2005–2011		H	NA	NA	NA	NA		NA	NA	NA
Uttar Pradesh							≤ 5	6–10	> 10				
	23	Singh S†	2009–2011	Lucknow	H	279	146	121	12		4.8 (4.7†)	57.4	2.2
	24	Kumar R	2009–2011	Agra	H	115	71	44	–		4.2	55.6	6
Assam							0–5	6–9	10–14	> 14			
	25	Nandi	1997–2002	Silchar	H	101	40	30	12	19	7.3	54.4	30
							≤ 4	5–9	10–14	> 14			
	26	Saikia	2009	Dibrugarh	O	13	0	1	1	11	21	8	NA
	27	Nath	2009	Dibrugarh	O	60	4	7	12	37	20	53.3	NA
	28	Das	2015–2016	Dibrugarh	O	10	0	0	3	7	15.5	30	10
Maharashtra							0–4	5–9	10–14	> 14			
	29	Khan*	2000–2005	Mumbai	H	30	NA	NA	NA	NA	NA	NA	73.3
	30	Dravid	2005–2007	Dhule & Malegaon	H	119	15	42	30	32	10.3	41.1	NA
							≤ 5	6–9	10–14	> 14			
	31	Phalkey	2011	Dhule	O	11	2	2	7	0	11	54.5	20
Karnataka							≤ 5	> 5					
	32	Basavraja	2015	Bangalore	H	31	8	23			7.3	48.3	48.4
	33	Dandinarsaiah	1997–2009	Hubli	H	52	21	31			6.6	46.2	11.5
	34	Parande*	2011	Belgaum	O	10		6 aged 5–12 y, 1 adult		NA	NA	NA	
	35	Havaldar§		Belgaum	H	97							
West Bengal							≤ 5	6–10	> 10				
	36	Halder	2004–5	Kolkata	H	107	27	31	49		9.4	50.5	NA
							0–9	10–19	> 19				
	37	Basak	2008–2012	Darjeeling	H	33	26	4	3		5.7	51.5	NA
	38	Kole§	2009–2011	Kolkata	H	200	NA	NA	NA		NA	NA	75%
Andhra Pradesh							0–4	5–9	6–14	> 14			
	39	Bitragunta	2003–2006	Hyderabad	H	2,685	124	455	530	1576	17.2	42.9	NA
							< 5	5–20	> 20				
	40	Meera Rao	2008–2012	Hyderabad	H	2,925	477	908	1540		21.6	60	40.8
	41	Jhancy	2013	Godavari	O	19	3	12	4		8.2	58	5
							≤ 5	6–10	> 10				
Rajasthan	42	Jain	2011–2014	Jaipur	H	180	87	66	27		6.2	63.3	19
Uttarakhand	43	Singh N	2005–2010	Nainital	H	48	NA	NA	NA		5	62.5	0
Chandigarh	44	Jayashri	1994–2002	Chandigarh	H	48	NA	NA	NA		5.2	NA	8.3
	45	Poddar	1998–1999	Chandigarh	H	7	7	0	0		3	42.8	28.9
Kerala	46	John*	1999–2001	Kerala	H	0	NA	NA	NA		NA	NA	NA

NA = not available; PCV = proportion of cases vaccinated.

* Age distribution not provided (*N* = 4) or no diphtheria cases were reported (*N* = 1).

† Mean/median age, as provided in the paper (*N* = 2).

‡ Provided overall incidence but not the age distribution (*N* = 1).

§ Full text was not available (*N* = 2).

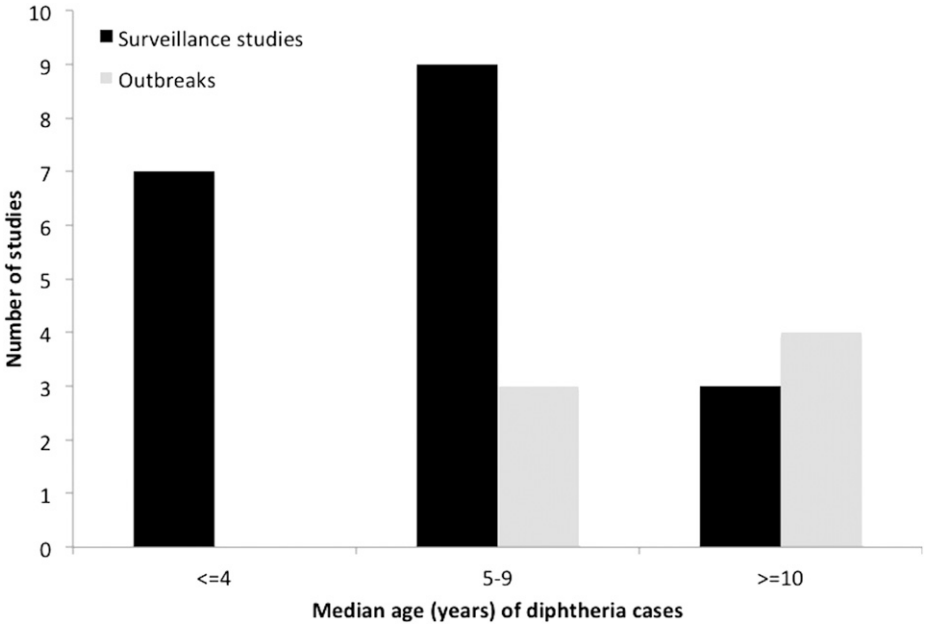

FIGURE 3. Median age of diphtheria cases reported in surveillance studies and outbreaks, India, 1996–2016.

Of the 26 studies, the median age of diphtheria cases was ≤ 4 years in seven studies/outbreaks, between 5–9 years in 12, and ≥ 10 years in 7 studies (Table 1, Figure 3). The median age of diphtheria cases in all studies from Delhi conducted over a period of 1997–2014 and Uttar Pradesh conducted during 2009–2011 was less than 5 years. One study each from Gujarat (1999–2002) and Chandigarh (1998–1999) also had the median age of cases to be < 5 years; however, other studies from these states during the subsequent period had the median age of cases ranging between 5 and 9 years. In all other studies from Andhra Pradesh, Assam, Chandigarh (1994–2002), Karnataka, Maharashtra, Rajasthan, Uttarakhand, and West Bengal, more than 50% of the diphtheria cases were aged ≥ 5 years (Table 1).

In Hyderabad, the incidence of diphtheria was higher among females (20 per 100,000 compared with 15 per 100,000), in Delhi the incidence was not different by sex. The proportion of males among diphtheria cases in different studies ranged between 40% and 62.5% (Table 1).

Religion. Diphtheria incidence in Hyderabad was found to be three times higher among Muslims (27 per 100,000) as compared non-Muslims (9 per 100,000). In Delhi, about 38% of the diphtheria cases were Muslims. Other studies however did not report the religion of diphtheria cases.

Diphtheria vaccination status of cases. Majority of diphtheria cases reported by hospital-based surveillance studies as well as during outbreaks were unvaccinated or partially vaccinated (Table 1).

Diphtheria vaccination coverage in India. According to the national level surveys, the coverage of three primary diphtheria vaccines ranged between 55.1% (1998–1999) and 78.4% (201–2016) (Figure 4).[6–13] The national level surveys however do not estimate the coverage of diphtheria boosters. Only one study in Hyderabad conducted during 2005–2006, had evaluated the coverage of first and second doses of diphtheria boosters. The findings of this study indicated that the coverage of three primary doses, first and second booster was 90% (95% confidence interval [CI]: 86–93), 60% (95% CI: 54–66), and 36% (95% CI: 27–40), respectively.[47] Although the coverage of primary immunization was not different among Muslim and non-Muslim children, booster coverage was significantly lower among Muslims.[47]

Population immunity against diphtheria. Only Five published studies describing the diphtheria immunity in different age groups were available. The study by Murhekar and others, conducted during 2008, covering more than 2,400 school children aged 6–17 years studying the various government schools in Hyderabad, found 56% children to be sero-protected with IgG antidiphtheria titers of 0.1 IU/mL or more, whereas 39% children were partially sero-protected with antibody titers between 0.01 and 0.1 IU/mL, whereas 6% children were susceptible.[47] A study conducted in in Delhi during 1993–1995, among 171 pregnant women aged 18–38 years found 94% women to have high antitoxin titers indicating boosting of immunity on account of continued transmission of diphtheria.[48] Another study conducted among 255 randomly selected healthy adults aged 20–55 years during 2009 indicated that 53% were unprotected.[49] A study among 210 children aged 4-6 years in Jalna District of Maharashtra indicated that 18% had no protection, whereas 12% were minimally protected (antibody titers between 0.01 and 0.1 IU/mL).[50] A study among 62 adults in Pune, Maharashtra, indicated 89% to be sero-protected.[51]

DISCUSSION

The findings of our review indicate that diphtheria continues to be a public health problem in India, with 10 Indian states accounting for most of the reported cases. The median age of diphtheria cases in most of the published studies was ≥ 5 years. In some Indian states, Muslim children were affected more. Most of the diphtheria cases were unvaccinated. The coverage of primary diphtheria vaccine in the country is around 80%, whereas the coverage of diphtheria boosters, although not available, is expected to be low.

The age distribution of diphtheria cases reflects the immunity status of the population. Long-term surveillance studies from

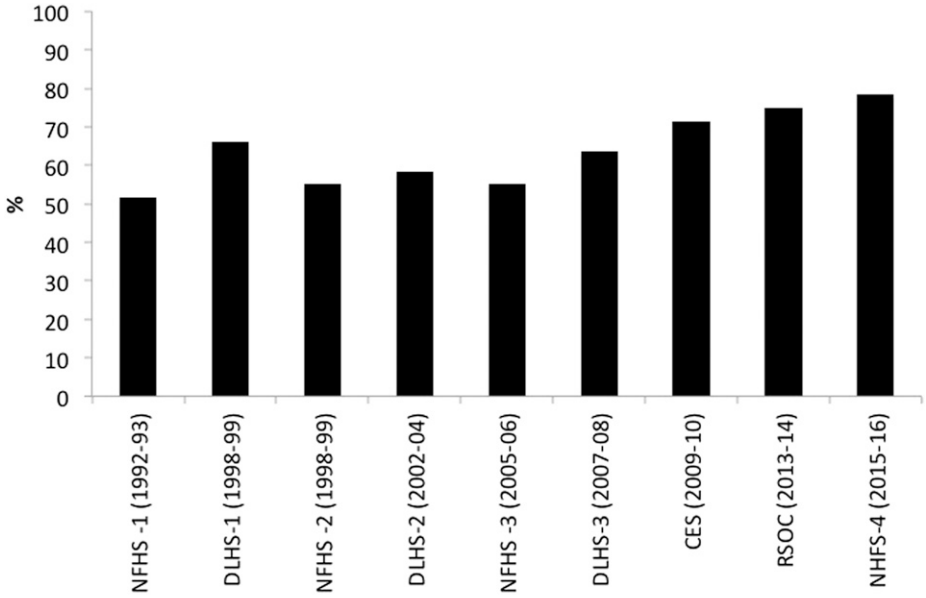

FIGURE 4. Proportion of children vaccinated with three primary doses of diphtheria vaccine in India as per national levels surveys.

different geographical regions (states) are required to document changing age distribution. Although such studies are lacking in India, comparison of the published studies within a state over a period of time suggested that in eight states, majority of the cases were among school-going children and adolescents, whereas in states of Delhi and Uttar Pradesh, most of the cases were among under-five children. Occurrence of diphtheria cases in under-five children reflects low coverage of primary diphtheria vaccination. During the prevaccination era globally as well as during eighties in India, high proportion of cases were under-fives.[3,52] Higher median age of diphtheria cases in most of the studies in India, indicates susceptibility of school-going and adolescent children to diphtheria either on account of low coverage of diphtheria vaccines as well as declining immunity acquired by vaccination or naturally.[1–3]

The available data on diphtheria have several limitations: First, the diphtheria cases reported to CBHI and WHO are likely to be underestimated and hence may not reflect the true burden of disease in India. Second, India does not have a case-based surveillance system covering all the states. The Integrated Disease Surveillance Program ongoing in all the States is limited by underreporting and lack of facilities for laboratory diagnosis. The published surveillance studies reflect the diphtheria situation at the level of Medical College or infectious disease hospital and might not reflect the situation in the country. Third, most of the surveillance studies describe the proportion of diphtheria cases in different age groups and did not estimate incidence of diphtheria.

A number of recommendations could be proposed for improving diphtheria control in India. First, the coverage of primary and booster diphtheria vaccinations administered as a part of Universal Immunization Program, needs to be improved. A special emphasis need to be given to increase the vaccine coverage among Muslim children in states such as Andhra Pradesh. Second, the immunity of school-going children could be improved by administering all the children with adult type of tetanus and diphtheria (Td) vaccine at school entry and replacing the tetanus toxoid vaccine used in school health program with Td vaccine; since the full potency diphtheria toxoid (25 Lf per dose) used in the Universal Immunization Program is associated with high reaction rates among older children and adults.[2] Third, a good surveillance is needed to document the impact of vaccination. A case-based surveillance is being implemented in few Indian states with support from the World Health Organization - National Polio Surveillance Project (WHO-NPSP). Extending this surveillance to other states will be useful to guide the immunization program. Fourth, the national level surveys need to include information about diphtheria boosters, besides the information about primary vaccination. Fifth, it is also necessary to conduct sero-surveys in all the states covering different age groups to estimate the population immunity guide the immunization program.

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