Epidemiol. Infect. (1999), **123**, 209–215. Printed in the United Kingdom

Diphtheria is declining but continues to kill many children: analysis of data from a sentinel centre in Delhi, 1997

J. SINGH*[1], A. K. HARIT[1], D. C. JAIN[1], R. C. PANDA[2], K. N. TEWARI[3], R. BHATIA[1] AND J. SOKHEY[1]

[1] *National Institute of Communicable Diseases, 22 Shamnath Marg, Delhi-110054, India*
[2] *Infectious Diseases Hospital, G. T. B. Nagar, Delhi-110009*
[3] *Director of Health Services-cum-Municipal Health Officer, Municipal Corporation of Delhi, Town Hall, Delhi-110006*

(*Accepted 7 May 1999*)

SUMMARY

Although diphtheria is declining in Delhi, case fatality rates (CFRs) are rising. In 1997, of 143 clinically suspected cases admitted to the Infectious Diseases Hospital 45 (32%) died. We examined their records to understand the epidemiology and reasons for high CFRs. About 53% of cases were from Delhi; they were not limited to any particular area. All the deaths and 92% (131/143) of cases occurred in children below 10 years of age. Only 12% of cases had received one or more doses of DPT. Muslims contributed significantly more cases than Hindus. CFRs were significantly higher in young ($P = 0{\cdot}03$) and unvaccinated ($P = 0{\cdot}01$) children and in those who received antitoxin on the third day of illness or later ($P = 0{\cdot}03$). The study highlights the importance of improved vaccine coverage and early diagnosis and prompt administration of antitoxin in reducing CFRs for diphtheria in Delhi.

INTRODUCTION

Diphtheria has long been endemic in Delhi and other parts of India [1–10]. Extensive Schick test surveys carried out in Punjab [2] and Uttar Pradesh in the early 1960s [3] revealed that the majority of persons became Schick test negative (immune to diphtheria) by 10 years of age. To make available large quantities of DPT vaccine required to control the disease, the Central Research Institute, Kasauli started production of DPT in 1964. This increased to about 2 million doses in 1968, and further to 5 million doses in 1970. At present, India is self sufficient in the production of DPT and DT vaccines.

The vaccine was made available to all the children in the country through the Expanded Programme on Immunization (EPI) in 1978. The reported coverage levels for three doses of DPT increased to about 41% in 1985–6 and further to about 90% in the early 1990s [11]. Reported coverage levels were, however, shown to be overestimated in many parts of the country by immunization coverage surveys [12]. Although the reported data on morbidity are also deficient, the trends indicate that the disease declined tremendously with the increase in vaccine coverage levels. The reported incidence declined from 4·3 per 100000 population in 1975–9 to 1·7 per 100000 population in 1985–9 and further to 0·9 per 100000 population in 1990–4 (authors' calculations using reported data).

Vaccine coverage levels have increased and the incidence of disease has decreased in Delhi also. A survey carried out in east Delhi (population > 2 million) in the last months of 1996 estimated that about 81, 74 and 69% of 12–23 months old children had received 1, 2 and 3 doses of DPT respectively (NICD, unpublished data). Based on the data on

* Author for correspondence.

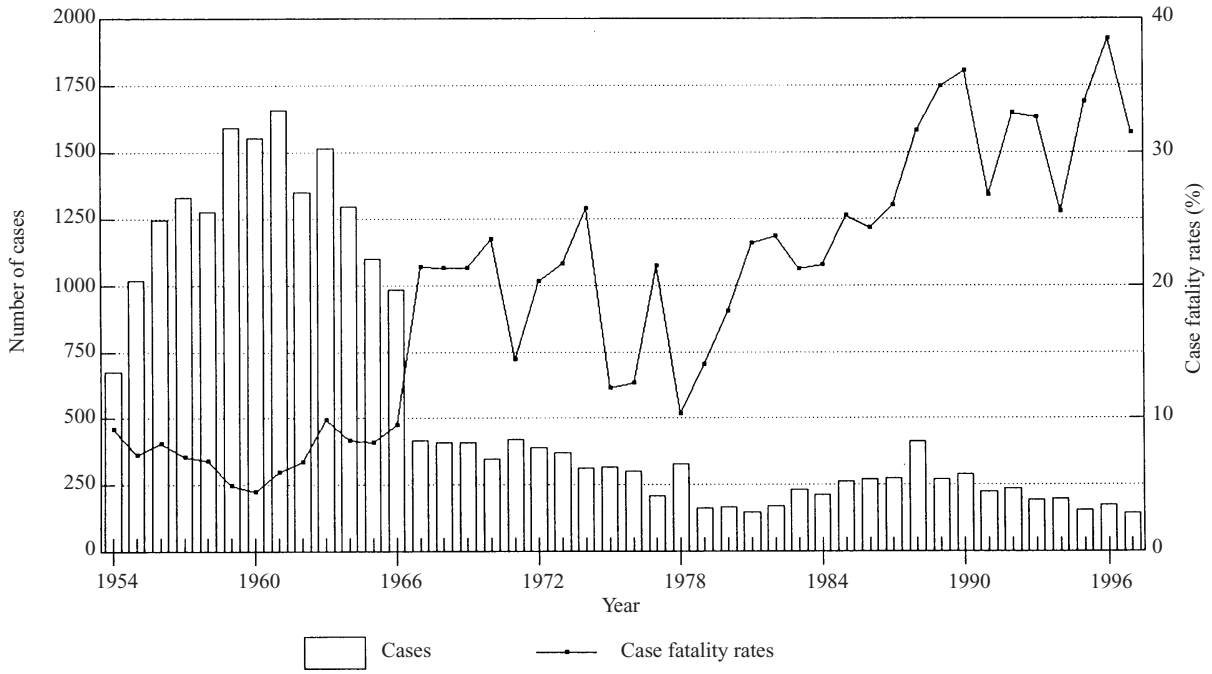

Fig. 1. Clinical diphtheria in Infectious Diseases Hospital, Delhi, 1954–97.

hospitalized cases, the incidence of clinical diphtheria was estimated to be about 54 per 100000 in 1954–62 [13]; the incidence declined to about 2 per 100000 population in 1980–4 and to about 1 per 100000 population in 1993–7 (authors' calculations using reported data).

However, despite a substantial decline in the number of the hospitalized cases in Delhi, case fatality rates (CFRs) have risen in the last four decades (Fig. 1). We analysed the clinical record sheets of cases admitted to the Infectious Diseases Hospital, Delhi (IDH) in 1997 to understand the epidemiology of diphtheria in general and the reasons for high CFRs in particular.

MATERIALS AND METHODS

In Delhi (population 9420644: 1991 census), all the clinically suspected cases of diphtheria are referred to the IDH for appropriate management [14]. Many cases from the surrounding districts are also admitted to the IDH every year.

Clinical record sheets of 155 patients admitted to the diphtheria ward of IDH in 1997 were studied; 12 of them were not considered as having diphtheria by the treating physicians and/or the authors on review of clinical features and availability of an alternative diagnosis. These were removed from the analysis. Clinicians diagnosed the cases on the basis of clinical features alone. The cases were considered to have nasal involvement if they had serosanguineous discharge and laryngeal involvement if they had hoarseness and stridor.

Throat swabs were collected on Loeffler's media from all cases and transported to the laboratories of the National Institute of Communicable Diseases (NICD) which is situated about 5 km from IDH. Standard methods were followed for isolation and identification of *Corynebacterium diphtheriae*. The strains were biotyped with the help of morphology, cultural characteristics and biochemical reactions. The strains were not tested for toxigenicity.

Clinicians ascertained the immunization status of the cases mainly on the basis of history. In most of the situations, number of doses received were not mentioned in the case sheets. While entering the data, it soon became apparent that a large number of patients with Muslim names were admitted to the IDH in 1997. We therefore, analysed the data by religion also. There was no mention of religion of patients in clinical record sheets. Names of the patients and their fathers provided the clue to the identity of their religion.

The records were analysed using Epi Info version 6.02. Differences between the proportions were determined by the χ^2 test. A P value of less than 0·05 was considered to be significant.

https://doi.org/10.1017/S0950268899002812

Table 1. *Epidemiological characteristics of diphtheria cases in and around Delhi, 1997*

Characteristic	No. of cases	% of total cases	No. died	CFR (%)
Age (years)				
< 1	20	14	10	50
1–4	73	51	22	30·1
5–9	38	26·6	13	34·2
10 or more	12	8·4	0	0
Sex				
Male	90	62·9	27	30
Female	53	37·1	18	34
Residence				
Delhi	76	53·1	24	31·6
Outside*	67	46·9	21	31·3
Religion				
Hindu	89	62·2	25	28·1
Muslim	54	37·8	20	37
Vaccination status				
Vaccinated	15	10·5	1	6·7
Unvaccinated	114	79·7	43	37·7
Not mentioned	14	9·8	1	7·1
Total	143	100·0	45	31·5

* Most of cases were from Bulandsahar (14), Meerut (12), Ghaziabad (12), and Muzaffarnagar (8) districts.

RESULTS

In 1997, 143 cases suspected of having diphtheria clinically were admitted to the IDH, of which 45 (31·5%) died. Two cases were readmitted with post diphtheric sequelae. Epidemiological characteristics of the cases are described in Table 1.

About 53% (76/143) of cases were from Delhi. This gave an incidence of about 0·65 per 100000 population. The remaining cases came from 12 nearby districts in Uttar Pradesh (56/143 = 39%), 5 districts in Haryana (10/143 = 7%) and 1 district in Rajasthan. The cases were scattered widely in Delhi as well as other districts. Only two patients (aged 2 and 7 years), affected within a period of 2 days, belonged to one family. CFRs were similar whether patients belonged to Delhi or other states.

All the deaths and 92% (131/143) of cases occurred in children below 10 years of age. Age distribution was similar whether patients were from Delhi or other states. Considering only cases which were residents of Delhi, the age-specific incidence was found to be 4·73, 2·93, 1·54 and 0·09 per 100000 population in < 1, 1–4, 5–9 and ⩾ 10 year age groups respectively. The age-specific CFRs were found to be the highest in infants and declined thereafter. While half of the infants (10/20) died, no death was observed in children 10 years or older ($P = 0·03$).

Although males were 54% (41/76) of cases from Delhi, the incidence was not different in the two sexes (males: 0·64 per 100000 population; females: 0·66 per 100000 population). In contrast, 73% (49/67) of cases which came from outside were males. Nevertheless, CFRs did not differ significantly between the two sexes.

Cases occurred all year but most often during the monsoon and post-monsoon months. About 74% (106/143) of cases occurred between July and November. Only 12% (17/143) of the cases were recorded during winter months (i.e., December, January and February) (Fig. 2).

More than 35% of cases from Delhi (27/76) and 40% from other areas (27/67) occurred in the Muslim population. The CFRs were higher in Muslims (20/54 = 37%) than in Hindus (25/89 = 28·1%) but, not significantly so ($P = 0·3$).

Immunization histories were available for only 129 cases. Only 15 (12%) of them had received one or more doses of DPT. The remaining 114 (88%) children were totally unvaccinated. Only one child who had received DPT (2 doses only) died, while 43 of 114 (37·7%) unvaccinated children died. CFR was

https://doi.org/10.1017/S0950268899002812

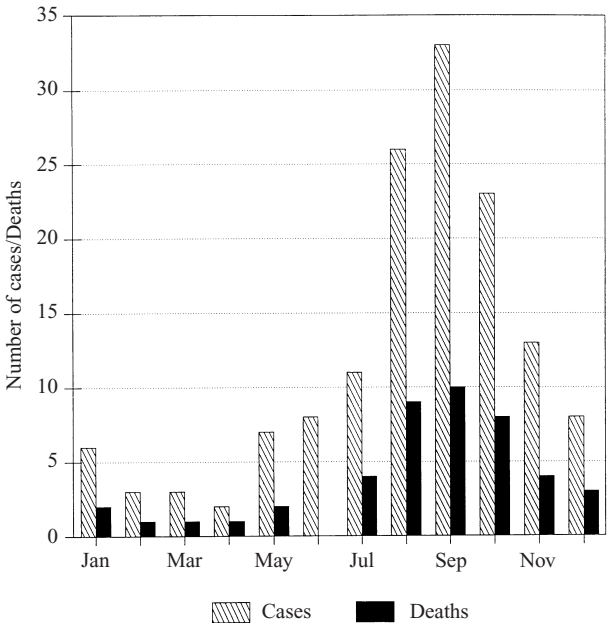

Fig. 2. Seasonality of clinical diphtheria in Delhi, 1997.

significantly higher in unvaccinated children ($P = 0{\cdot}01$).

The cases were also analysed by clinical presentation and duration of illness before admission to the IDH. The results are shown in Table 2. All patients presented with symptoms of acute respiratory infection. About 84% (120/143) cases had a well demarcated pseudomembrane and 19 (13·3%) patients presented with a bullneck. About 17·5% (25/143) of cases had involvement of the larynx in addition to the throat; three additional cases were considered having only laryngitis. The remaining 96 cases had either pharyngeal ($n = 92$) or nasopharyngeal ($n = 4$) diphtheria. The CFRs were significantly higher in cases having bullneck diphtheria ($10/19 = 52{\cdot}6\%$) than in cases having pharyngeal or nasopharyngeal ($26/96 = 27{\cdot}1\%$) diphtheria ($P = 0{\cdot}03$). CFRs were intermediate in children having laryngeal involvement ($9/28 = 32{\cdot}1\%$). Twenty three children (16%) had signs of obstruction when admitted to the IDH. Four of them needed tracheostomy. Two cases developed palatal paralysis, while one had neuritis (9th nerve). One patient each developed nephritis and thrombocytopenia. Physicians suspected myocarditis on clinical grounds in eight patients who died. Electrocardiograms were not available with the records. None of the 13 children who had been fully vaccinated (3 or more doses of DPT) before illness developed bullneck diphtheria, myocarditis, respiratory obstruction, or other fatal complications.

All the cases were administered diphtheria antitoxin after admission in the IDH. While none of the 4 children who were admitted to the IDH (and administered diphtheria antitoxin) on the first day of illness died, 2 of 18 (11·1%) cases who were admitted on the second day of illness died. In contrast, about 38% (40/105) of children who were admitted to the IDH on the third day of illness or later died. The differences were highly significant ($P = 0{\cdot}03$).

Median duration of hospitalisation in IDH was 7 days (range 4–16) in cases who recovered and 1 day (range 0–11) in those who died. Most of the deaths ($31/45 = 68{\cdot}9\%$) occurred within 2 days of admission.

Throat swabs from all the cases were processed in the laboratories of NICD for isolation of *C. diphtheriae*; 21 of 143 cases (14·7%) were positive. *C. diphtheriae* positive cases were in no way different from negative cases.

DISCUSSION

Although DPT vaccine does not provide complete protection against clinical diphtheria, the disease, if occurs, is usually mild and rarely fatal in immunized persons [15, 16]. As shown in Table 1, only 1 of 45 children who later died had been immunized against diphtheria (2 doses of DPT). CFR was significantly higher in unvaccinated (37·7%) than in vaccinated (6·7%) children ($P = 0{\cdot}01$). The results confirmed the importance of immunization in preventing diphtheria mortality also.

Many studies have shown the occurrence of diphtheria cases in older persons when the vaccination coverage improved [17–19]. The age distribution of diphtheria cases admitted to the IDH in 1997 did not differ from that observed in previous years [14, 20, 21]. The disease continued to affect mainly young children, especially those who remain unvaccinated. It seems that the vaccine coverage levels are not sufficiently high in Delhi and surrounding areas to change the epidemiology of diphtheria. Recent vaccine coverage surveys have also revealed only moderate coverage levels in Delhi [1]. Thus there is a need to achieve and maintain high immunization coverage levels in children to reduce the circulation of *C. diphtheriae* in the community.

Many studies have shown a low risk of death due to diphtheria if the antitoxin is administered early [15]. It was found true in this study also. As shown in Table 2, none of the 4 children died if admitted to the IDH

https://doi.org/10.1017/S0950268899002812

Table 2. *Clinical characteristics of diphtheria cases in and around Delhi, 1997*

Characteristic	No. of cases	% of total cases	No. died	CFR (%)
Duration of illness before hospitalization (days)				
1	4	2·8	0	0
2	18	12·6	2	11·1
3 or more	105	73·4	40	38·1
Not mentioned	16	11·2	3	18·8
Type of diphtheria				
Pharyngeal	92	64·3	26	28·3
Nasopharyngeal	4	2·8	0	0
Laryngopharyngeal	25	17·5	8	32·0
Primary laryngeal	3	2·1	1	33·3
Bullneck	19	13·3	10*	52·6

* Two more cases left the hospital in critical condition against medical advice.

(and administered diphtheria antitoxin) on the first day of illness. Only 2 of 18 (11·1%) cases died who were admitted on the second day of illness. In contrast, about 38% (40/105) of children died who were admitted on the third day of illness or later. The differences were significant ($P = 0{\cdot}03$). If administration of antitoxin is so critical for the survival of diphtheria cases, why are cases not getting it early? Either parents do not seek early treatment for their sick children or the clinicians outside do not suspect diphtheria in these cases. At least 70 cases were referred to the IDH by other hospitals, both government and private, and family physicians. Most of these cases were prescribed drugs, mostly antibiotics, for respiratory symptoms. Diphtheria was only suspected when they did not respond to the treatment. Although nothing was mentioned in the case sheets about other patients, we believe that most of them also had similar experience. This explains the low isolation rates of *C. diphtheriae* from throat swabs of cases (see below). Once diphtheria was suspected, these cases were referred to the IDH without administering diphtheria antitoxin. IDH is perhaps the only hospital in Delhi, which stores and administers antitoxin. The study indicates the need to educate private as well as government doctors to keep a high degree of suspicion for diphtheria in Delhi and surrounding areas, especially in unvaccinated children, and refer these patients early to the institutions where antitoxin is available. All major hospitals should store and administer antitoxin to the suspected cases. If they do not store antitoxin, which is perhaps the case at present, they must refer the cases immediately to the IDH to prevent mortality.

Although cases occurred round the year, most of them occurred during monsoon and postmonsoon months. The seasonality of disease has not changed in Delhi over the years [13, 14, 20, 21] and the disease has been found to be highly prevalent in the same seasons in other areas also [4–6, 22]. In contrast, diphtheria is predominantly a disease of colder months in temperate climates [23]. The difference may be due to the high prevalence of cutaneous diphtheria in tropical countries including India, especially in the hot and humid season [24–26]. Persons with cutaneous diphtheria have been shown to frequently transmit the infection to others [27]. Thus the seasonal pattern of diphtheria in Delhi is consistent with the important role of cutaneous diphtheria in the spread of infection in the community.

Misdiagnosis, prior treatment of children with antibiotics, or poor specimen handling may affect isolation of *C. diphtheriae* from suspected cases. Almost all the cases for whom the information was available had received antibiotics before admission to the IDH. Therefore, administration of antibiotics before hospitalization was perhaps the major factor responsible for isolation of *C. diphtheriae* from only 15% (21/143) of the cases in 1997. A review of historical data from the laboratories of NICD revealed that isolation rates of *C. diphtheriae* ranged from 0% to about 10% during 1978–96. Although

https://doi.org/10.1017/S0950268899002812

antibiotics help in reducing the transmission to other persons, there is no effect on toxin already elaborated or absorbed [23]. Prompt administration of antitoxin is essential to neutralize the toxin and prevent mortality.

Analysis of the cases by religion revealed that more than 35% of cases from Delhi (27/76) and 40% from other areas (27/67) occurred in the Muslim population. In contrast, Muslims constitute only 9% of total population in Delhi, 17% in Uttar Pradesh and 5% in Haryana (1991 Census). Although the CFRs were not significantly higher in the Muslims (20/54 = 37%) than in Hindus (25/89 = 28·1%) ($P = 0{\cdot}3$), there were significantly more cases (and deaths) in Muslims than Hindus. The results indicate the existence of pockets with comparatively poor vaccination coverage. This is an area of serious concern and calls for spot mapping of cases and monitoring of immunization coverage levels by sub-units to identify high risk pockets.

In conclusion, the results showed that diphtheria continues to affect the children in Delhi, especially those who remain unvaccinated and that CFRs are significantly higher in young ($P = 0{\cdot}03$) and unvaccinated ($P = 0{\cdot}01$) children and in those who are admitted to the IDH (and administered diphtheria antitoxin) on the third day of illness or later ($P = 0{\cdot}03$). The study indicated the need to improve vaccine coverage levels with special attention to high risk pockets, to store antitoxin in all major hospitals, and to suspect diphtheria in the early part of illness to allow administration of antitoxin in time to reduce morbidity and mortality rates.

REFERENCES

1. Singh J, Ichhpujani RL, Prabha S, et al. Immunity to diphtheria in women of childbearing age in Delhi in 1994: evidence of continued *Corynebacterium diphtheriae* circulation. Southeast Asian J Trop Med Public Health 1996; **27**: 274–8.
2. Suri JC, Grewal HS, Khosla SL, Dhillon H. Schick test survey in Punjab. Indian J Med Res 1967; **55**: 179–84.
3. Chandra R, Bhatnagar JK, Prasad BG, Khan AM, Jain PC. A study of immunity status against diphtheria among children below five years in a rural population in Lucknow district. Indian J Med Res 1971; **59**: 1666–75.
4. Basappa K. Epidemiological study of diphtheria in retrospect. J Indian Med Assoc 1963; **41**: 397–400.
5. Singha P, Taylor W. Diphtheria in Nagpur, 1951–58. Indian J Public Health 1959; **3**: 337–44.
6. Chakraborty AK, Das KB, Bose R. Trends of diphtheria in Calcutta. Indian J Public Health 1986; **30**: 188–92.
7. Deodhar NS, Gracias R. Susceptibility to diphtheria among the primary school children in Poona. Indian J Med Sci 1968; **22**: 85–7.
8. Basu RN. Surveillance of diphtheria. In: Basu RN, ed. Sentinel surveillance. Delhi: National Institute of Communicable Diseases, 1985: 24–8.
9. Marathe SN. Downward trend of diphtheria in Bombay. In: Basu RN, ed. Sentinel surveillance. Delhi: National Institute of Communicable Diseases, 1985: 33–5.
10. Murthy LS. Trend of diphtheria in Bangalore. In: Basu RN, ed. Sentinel surveillance. Delhi: National Institute of Communicable Diseases, 1985: 29–32.
11. Ministry of Health and Family Welfare. Maternal and Child Health Programme. Annual Report, 1996–97. Delhi: Ministry of Health and Family Welfare, 1997: 25–32.
12. Ministry of Health and Family Welfare. Evaluation of vaccination coverage. CSSM review, June 1995: 4–6.
13. Patnaik KC, Kapoor PN. Some observations on diphtheria in Delhi. Indian J Public Health 1967; **11**: 82–7.
14. Ray K, Dutta KK, Mukherjee AK, Anand BR, Chowdhuri ANR. Hospital based surveillance of faucial diphtheria in and around Delhi. Indian J Med Res 1983; **78**: 776–9.
15. Mortimer EA. Diphtheria toxoid. In: Plotkin SA, Mortimer EA, eds. Vaccines, 2nd ed. Philadelphia: W. B. Saunders Company, 1994: 41–56.
16. Munford RS, Ory HW, Brooks GF, Feldman RA. Diphtheria deaths in the United States, 1959–1970. JAMA 1974; **229**: 1890–3.
17. Khuri-Bulos N, Hamzah Y, Sammerrai SM, et al. The changing epidemiology of diphtheria in Jordan. Bull WHO 1988; **66**: 65–8.
18. Loevinsohn BP. The changing age structure of diphtheria patients: evidence for the effectiveness of EPI in the Sudan. Bull WHO 1988; **68**: 353–7.
19. Galazka AM. The immunological basis for immunization, Diphtheria. Expanded Programme on Immunization, World Health Organization, 1993. WHO document WHO/EPI/GEN/93.12.
20. Shastri LP. Trend of diphtheria in Delhi. In: Basu RN, ed. Sentinel surveillance. Delhi: National Institute of Communicable Diseases, 1985: 39–42.
21. Dutta JK, Ayyagari A, Gautam AP, Chadha SK, Ray SN. A comparative study of bacteriologically proved and clinically diagnosed (culture negative) cases of diphtheria. J Indian Med Assoc 1976; **67**: 241–5.
22. Chakraborty SM. The incidence and treatment of faucial diphtheria in a rural West Bengal population. J Indian Med Assoc 1970; **55**: 371–5.
23. Wehrle PF. Diphtheria. In: Evans AS, Brachman PS, eds. Bacterial infections of humans, 2nd ed. New York: Plenum Medical Book Company, 1991: 227–37.
24. Ayyagari A, Venugopalan A, Ray SN. Studies on

diphtheria infection in and around Delhi. J Indian Med Assoc 1975; **65**: 328–31.
25. National Institute of Communicable Diseases. Prevalence of *C. diphtheriae* in skin lesions. Annual Report, 1982. Delhi: National Institute of Communicable Diseases, 1982: 104.
26. National Institute of Communicable Diseases. Studies on cutaneous diphtheria from Nand Nagari PHC, Delhi. Annual Report, 1984. Delhi: National Institute of Communicable Diseases, 1984: 98.
27. Belsey MA, LeBlanc DR. Skin infections and the epidemiology of diphtheria: acquisition and persistence of *C. diphtheraie* infections. Am J Epidemiol 1975; **102**: 179–84.