

Original Research Article

Re-emergence of diphtheria in Kerala: the need for change in vaccination policy

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Received: 10 December 2018

Accepted: 12 January 2019

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ABSTRACT

Background Diphtheria cases continue to occur in India despite a national vaccination program targeting the disease. Outbreaks of diphtheria have been known to occur in areas of low immunization coverage. An age shift has been noted to older children and adults in recent outbreaks from the Indian states of Andhra Pradesh, Karnataka, Delhi and Assam. Kerala witnessed its largest outbreak of diphtheria in recent times from 2015 to 2017.

Methods: Surveillance data from the Regional PEID cell during the outbreak period was analysed and epidemiological data generated.

Results: A total of 734 cases of diphtheria were reported during this period with eight deaths (Case fatality rate=1.08%). The mean age of the cases was 17.4 years (± 13.9). More than 72% of the cases occurred in children above 10 year of age and 68% of the cases were either unimmunized or partially immunized. 32% of the cases were immunized for age. Of these, immunized children, 88% were above 10 years of age, indicating waning immunity with age. The existence of a sizeable unimmunized cohort in the adolescent age group and waning immunity among immunized were two major factors contributing to the outbreak.

Conclusions: An age shift has been observed in the occurrence of diphtheria cases during the outbreak in Kerala. Booster doses with Td vaccine during adolescence in addition to maintaining a high immunization coverage in the routine immunization program, with special emphasis on pockets of low coverage is essential for preventing the reemergence of diphtheria.

Keywords: Age shift, Diphtheria outbreak, Td vaccine

INTRODUCTION

Diphtheria is an infectious disease of acute onset caused by the bacterium *Corynebacterium diphtheria*, which primarily infects the throat and upper airways. The exotoxin produced by the bacteria causes a membrane of dead tissue to build up over the throat and tonsils, making breathing and swallowing difficult.¹ The toxin affects organs like the heart and nervous system causing myocarditis or peripheral neuropathy in severe cases. The disease is characterized by sore throat, low-grade fever

and cervical lymphadenopathy. Death can occur due to circulatory failure during the first 10 days of the illness.²

Introduction of diphtheria toxoid in vaccination programs has reduced the mortality and morbidity of diphtheria dramatically the world over. However, diphtheria is still a significant child health problem in countries with poor immunization coverage.¹ In countries endemic for diphtheria, the disease occurs mostly as sporadic cases or as small outbreaks.¹

A major share of the diphtheria cases occurring in the world each year is from India. There has been a declining trend in new cases after the introduction of the Universal Immunization Program (UIP) in India. Still, around 2000 to 4000 cases get reported annually in the country.³ In the last decade, there have been reports of re-emergence of diphtheria from several states: Andhra Pradesh, Delhi, Maharashtra, Assam, Karnataka, Chandigarh, Gujarat and many of them presenting as outbreaks.⁴⁻⁸ Most of the outbreaks were characterized by cases in low immunization pockets.

Kerala, the southernmost state of India has high immunization coverage of 82% and better health indices when compared to the rest of India. Despite these favourable factors, outbreaks of diphtheria were reported from Kerala during three consecutive years-2015, 2016 and 2017. The outbreak began in the district of Malappuram in 2015 and spread initially to the neighbouring district of Kozhikode and later to other districts. Apart from the fact that the outbreak began in an area of low immunization coverage, another feature of interest was the age shift that was noted. In this article, we share the epidemiological details of this outbreak that was generated through a routine surveillance system and recommends an urgent modification in the national vaccination policy.

METHODS

Our Institution is a tertiary care center which serves as a referral center for five districts in Northern Kerala. We analysed the surveillance data from the onset of the outbreak in September 2015 to December 2017. The data was obtained from our Regional Prevention of Epidemics and Infectious Diseases Cell (RPEID Cell) which is part of a network of surveillance units established in all government medical colleges in Kerala and managed by the departments of Community Medicine in each college.

Case surveillance

Daily line list of “Probable and confirmed diphtheria cases” were collected from the medicine, pediatrics, infectious diseases and Ear Nose Throat (ENT) wards and outpatient department as part of surveillance activity during this period.⁹

Immunisation history

Details of immunization was elicited from individual cases and crosschecked with the immunization cards for children (≤ 15 years). Verbal history of immunization was relied upon, for adults. Those who had not received even one dose of the primary immunization series of DPT/Pentavalent vaccine were categorized as ‘unimmunised’. Those who had received at least one dose of diphtheria toxoid either as DPT/Pentavalent vaccine but not completed the WHO recommended schedule of 5 doses were categorized as ‘partially immunized’ and

those who had taken all 5 doses of the diphtheria toxoid were categorized as ‘fully immunized’. Those who could not recall their immunization status were also categorized as ‘unimmunized’.

Laboratory testing

Throat swabs for culture of *Corynebacteria* were taken soon after admission by trained medical officers and tested at the Microbiology Department of our institution. The throat swabs were processed and the isolate was identified by culture using 5% sheep blood agar and serum Tellurite agar. *C. diphtheriae* colonies were confirmed with the cystinase test growing black colonies with a brown halo on Tinsdale agar. Antibiotic sensitivity testing was performed using Kirby Bauer disc diffusion method on Mueller–Hinton blood agar plates. All isolates were sent to State Public Health Lab, Thiruvananthapuram, for Elek gel diffusion test and Tox gene demonstration by polymerase chain reaction.

RESULTS

The epidemic of diphtheria in Kerala began in September 2015 and continued till 2017. A total of 734 cases reported to our institution during this period with 8 deaths yielding a case fatality rate of 1.08%.

The index case

The first case brought to the notice of the health system was a 12 year old boy from a hostel (orphanage cum residential school) in Malappuram district, admitted to the pediatric ward of our institution on 7th September 2015 with toxic features and a membrane over the throat. *Corynebacterium* was cultured from the throat swab of the case.

The second case

This was from the same hostel was admitted with similar symptoms on 8th September 2015, and confirmed as diphtheria by throat swab culture. Despite treatment with antibiotics and antitoxin, the second case died on 17th September 2015.

The primary case

Death of a 13 year old boy residing in the same hostel occurred on 4th September 2015. The cause of death was retrospectively diagnosed as “Probable diphtheria” as per the CDC case definition of diphtheria.⁹ The primary case shared the same seating arrangements at school with the index case and the second case.

Surveillance

Following the confirmation of diphtheria, the District Medical Officer (DMO) of Malappuram was intimated and active surveillance of all close contacts of the

confirmed and probable cases were done. Throat swabs were taken from 28 probable cases out of which six were laboratory confirmed as diphtheria positive. As all the inmates of the hostel were unimmunized, they were immunized with 3 doses of Td vaccine (at 0, 1 and 6 months). Following strict control measures, no more cases were reported in the year 2015.

In the year 2016, cases of diphtheria started reporting in our institution from the month of May. As in the year 2015, the initial cases were from Malappuram district. Kozhikode district reported its first case in June 2016. Subsequently, more cases were reported from both Malappuram and Kozhikode districts and the outbreak continued with 411 and 295 cases reporting to our institution in 2016 and 2017 respectively (Table 2). Of the total 734 ‘probable diphtheria’ cases, 14% (106) were confirmed by throat swab culture (Figure 1). All the isolates were sensitive to Penicillin and Erythromycin and positive for toxgene.

Table 1: Diphtheria-case definition.

Probable	<p>In the absence of a more likely diagnosis, an upper respiratory tract illness with:</p> <ul style="list-style-type: none"> • An adherent membrane of the nose, pharynx, tonsils, or larynx; and • Absence of laboratory confirmation; and <p>Lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria</p>
Confirmed	<p>An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; and any of the following:</p> <ul style="list-style-type: none"> • Isolation of <i>Corynebacterium diphtheriae</i> from the nose or throat; or • Histopathologic diagnosis of diphtheria; or • Epidemiologic linkage to a laboratory-confirmed case of diphtheria.

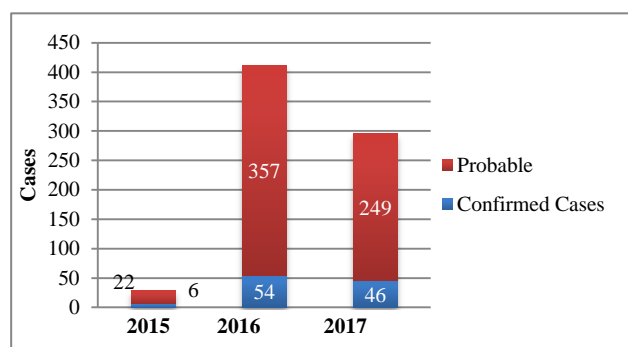


Figure 1: Diphtheria cases during outbreak.*

*Surveillance data from RPEID Cell Kozhikode

Control measures

Control measures were initiated immediately by the department of health services in the district of Malappuram and Kozhikode and other affected districts. Cases admitted in our institution were treated in a dedicated isolation ward with antitoxin, crystalline Penicillin and supportive care. Cases were kept in isolation for a minimum period of two weeks and discharged only after two consecutive throat swabs taken 24 hours apart were negative. Close contacts of the confirmed cases were immunized with diphtheria containing vaccine (Td or DPT) according to age and immunization status. Prophylaxis with Erythromycin was initiated for family contacts and close contacts of cases. Active measures to identify unimmunized/partially immunized children were initiated and school-based vaccination campaigns conducted to increase the immunization coverage in the age group 5 to 15 years.

Epidemiology

Cases were reported from 11 of the 14 districts in the state with maximum cases being reported from the districts of Kozhikode and Malappuram. Out of the total 734 cases, eight succumbed to the disease—case fatality rate 1.08%.

Seasonality of the outbreak was observed from the months of July to October with the maximum number of cases in the month of July (Figure 2).

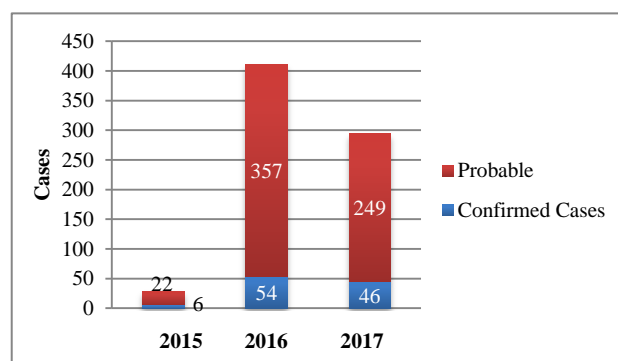


Figure 1: Diphtheria cases during outbreak.*

*Surveillance data from RPEID Cell Kozhikode

The mean age of the cases was 17.4 years (± 13.9), median age was 16 years (Range-6 months to 65 years). Majority of cases (35.6%) were seen in the age group of 10-20 years. More than 72% of the cases occurred in those more than 10 years of age (Table 3).

The number of males was marginally more than females (395, 53.8%) (Table 3). Males were more affected among children and adolescents (<20 years), but female predisposition was observed among adults (>20 years).

The breakup of diphtheria cases based on religion shows that most of them (71.5%) were from the Muslim community. As per 2011 census the district of Malappuram has a higher proportion of Muslims (70%).

Kozhikode too has a high share (39%) of muslim population. Even when the high distribution of muslim population in the districts is considered, the cases among the Muslim community were high.

Table 2: District wise and year wise diphtheria cases in North Kerala*

District/Year	Kozhikode	Malappuram	Kannur	Wayanad	Palakkad	Others	Total Cases
2015	-	28	-	-	-	-	28
2016	206	154	16	21	8	3	411
2017	132	98	22	40		3	295
Total	338 (46.1%)	280 (38.2%)	38 (5.2%)	61 (8.3%)	8 (1.1%)	6 (0.8%)	734 (100%)

*Surveillance data from regional PEID Cell Kozhikode

Table 3: Age and sex distribution of diphtheria cases.

Age group (years)	Females (%)	Males (%)	Total (%)
<5	17 (28.3)	43 (71.7)	60 (8.2)
5-10	51 (35.4)	93 (64.6)	144 (19.6)
10-20	94 (36)	167 (64)	261 (35.6)
20-30	83 (61.9)	51 (38.1)	134 (18.1)
30-40	57 (71.3)	23 (28.7)	80 (10.9)
>40	37 (67.3)	18 (32.7)	55 (7.5)
Total	339 (46.2)	395 (53.8)	734 (100)

Table 4: Age wise immunization status of diphtheria cases.

Age group (years)	Unimmunised (%)	Partially immunised (%)	Fully immunised (%)	Total (%)
<5	16 (5.4)	36 (18)	8 (3.3)	60 (8.2)
5-10	47 (15.8)	79 (39.5)	19 (8)	144 (19.6)
10-20	59 (19.9)	65 (32.5)	137 (57.8)	261 (35.6)
20-30	65 (21.9)	11 (5.5)	57 (24)	134 (18.1)
30-40	58 (19.5)	9 (4.5)	13 (5.5)	80 (10.9)
>40	52 (17.5)	0	3 (1.3)	55 (7.5)
Total	297 (40.5)	200 (27.2)	237 (32.3)	734 (100)

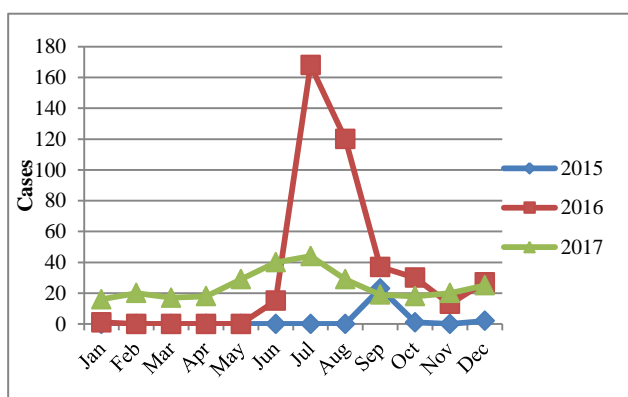


Figure 2: Seasonality of diphtheria cases.

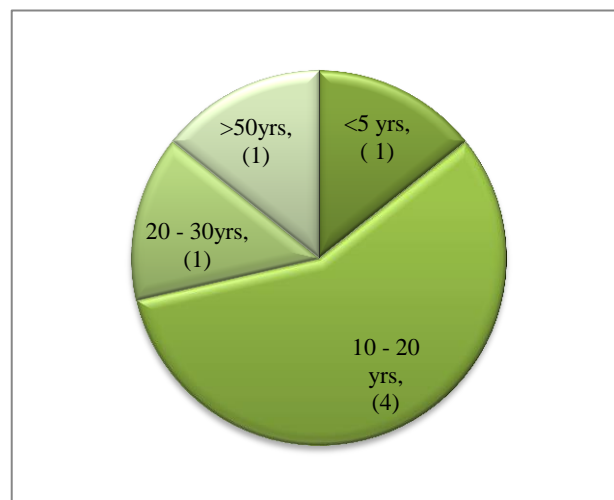


Figure 3: Age distribution of deaths.

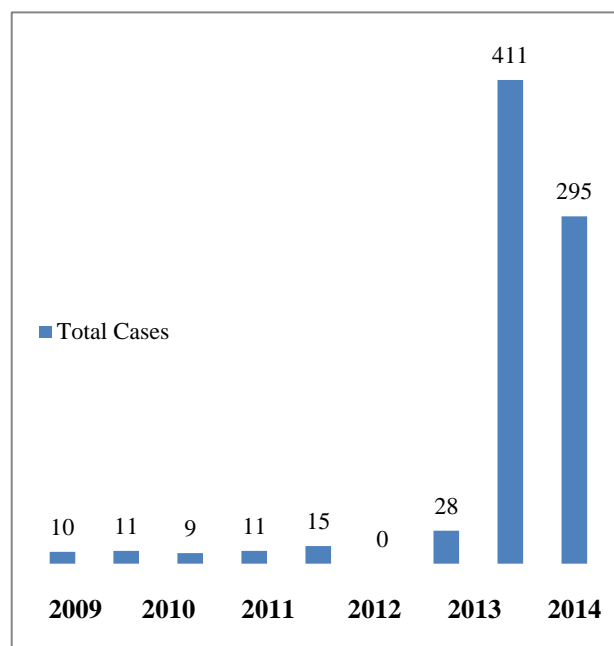


Figure 4: Diphtheria cases in north Kerala 2009 to 2017.

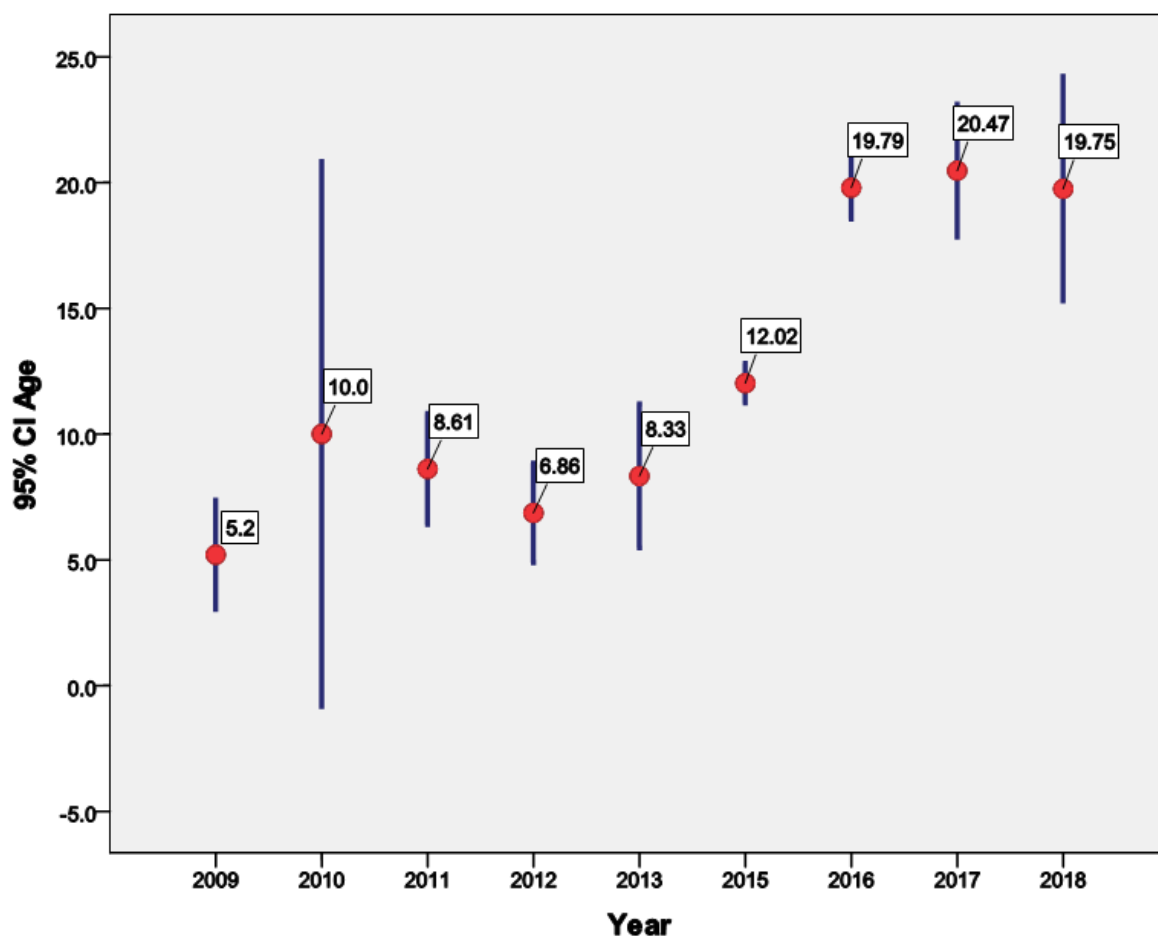


Figure 5: Mean age of diphtheria cases showing age shift.

More than 68% of the cases were either unimmunized or partially immunized (Table 4). Diphtheria was also seen in the fully immunized population. 32% of the cases were immunized for age but a majority of these (nearly 88%) were above 10 years of age, indicating waning immunity with age. Diphtheria was seen only among a small percentage of those immunized for age in the under-five age group (3.3%) and 5-10 year age group (8%) (Table 4).

Including the primary case, eight deaths occurred during the outbreak of which 7 were males. Most (4 deaths) were in the adolescent age (10-20 years) (Figure 3). All of them were unimmunized. The cause of death included myocarditis and septic shock.

DISCUSSION

The outbreak of diphtheria in Kerala which began in September 2015 and continued to 2017 was the largest outbreak in recent times in Kerala. As our institution is the tertiary care centre for Kozhikode and neighbouring districts and a dedicated diagnostic centre in North Kerala, more than 75% of the cases which occurred in the state were treated here. As seen from the surveillance data over the years the number of cases of Diphtheria

being reported annually has been low until 2015 when it re-emerged as a localised outbreak (Figure 4).

The outbreak began in a boy's hostel at Malappuram in 2015 which had inmates in the age group 10-15 years and all the inmates were either unimmunized or partially immunized. The outbreak which was localised in 2015 evolved into a major outbreak involving the neighbouring district of Kozhikode in the coming years. Outbreaks of diphtheria are usually associated with low immunization coverage. Even when Kerala displayed an immunization coverage of 82% for the primary vaccines as per NFHS 4 data, the same figure for Malappuram and Kozhikode districts were 70.6% and 70% respectively.¹⁰ The vaccination coverage as per NFHS 3 in Kerala was 75% and that of Malappuram and Kozhikode 63.9% and 65% respectively.¹¹ The NFHS data clearly shows the existence of a sizeable unimmunized/partially immunized cohort in these two districts which may have contributed to the outbreak. Acceptance of vaccination is an issue among certain sections of the community in North Kerala as has been observed by the media reports during the time of this outbreak.^{12,13} Interventions targeted at these high-risk pockets by mobilizing the community and local leaders will be helpful in bridging this gap to a great extent.

There has been a shift in the burden of disease to the adolescent age group in the outbreak as can be seen from the fact that more than 72% of the cases were above 10 years of age. Mean age of the reported cases in Kerala over the years has shown a gradual shift to the adolescent age from 5.2 years in the year 2009 to 20.5 years in 2017 (Figure 5). A shift in the age group has also been demonstrated internationally in outbreaks which have occurred in the Dominican Republic and Europe.^{14,15} Outbreaks in Andhra Pradesh reported age shift in cases where children above 10 years were increasingly affected.^{4,16} In an outbreak in Assam in 2009 only adults >20 years were affected.¹⁷ Reports from other states like Delhi, Haryana, West Bengal also indicate an age shift with cases increasingly being reported among the older children.^{5,18} Presence of an older unimmunized cohort and the waning of immunity to diphtheria during adolescence are factors responsible for the age shift of the disease to the adolescent age.

Majority of the cases in the current study were either unimmunized or partially immunized, which emphasizes the protection afforded by routine childhood immunization against diphtheria, especially among the very young. But the occurrence of diphtheria among immunized subjects in the older age group (>10 years) indicates waning of immunity with age. In addition, opportunities for boosting of antibody titre with subclinical infection were also low. This calls for additional booster doses of diphtheria toxoid during adolescence to maintain protective antibody titres against diphtheria. In India, diphtheria toxoid is given as 3 primary doses at 6, 10 and 14 weeks and boosters at 16-18 months and five to six years of age in the national immunization schedule. Replacement of Tetanus toxoid vaccine with tetanus and diphtheria toxoid (Td vaccine) at 10 years and 16 years will help in boosting the waning immunity.

Outbreaks of diphtheria are dependent on herd immunity of the population. Maintaining high routine immunization coverage in the Universal Immunisation Programme (UIP) and active measures to identify pockets of low immunization can ensure herd immunity is above the threshold level.

In the below 20yrs age group, males were mostly affected. But in the above 20 years age group, females were the ones more affected. Females above 20 years are caregivers for children and adolescents which places them at higher risk for contracting the disease, which might explain the high proportion of cases in this age group. Female preponderance in diphtheria has been reported from outbreaks in Andhra Pradesh whereas a study from Gujarat observed male preponderance among children.^{4,16,19}

The cases fatality rate in the current outbreak was only 1.08% which is considerably lower than the overall case

fatality rate of 2.2% for diphtheria observed in India.²⁰ Higher case fatality has been reported in Delhi (4.2%) and Assam (3.3%), Andhra Pradesh (3%).^{16,17,21} Prompt outbreak response by the health system and active surveillance ensured early diagnosis, isolation and treatment of cases and contacts which was the main reason for the low case fatality.

The main reason for this huge outbreak in Kerala was the presence of an unimmunized cohort of adolescent children which can be seen from the fact that it began in a closed community of a hostel where most of the children were unimmunized. Overcrowding and mixing of the population was another factor which could have resulted in the outbreak as the hostel also had inmates from other states. The persistence of diphtheria in the community in the form of subclinical infection and carriers resulted in the outbreak continuing in the subsequent years. A waning of immunity in the adolescent age among those already immunized further added to the outbreak. Currently (in 2018), diphtheria cases are still being reported in our institution, the number of cases have come down to 77 cases but surveillance is continuing and the epidemic may wane in the coming years.⁶

CONCLUSION

There has been a re-emergence of diphtheria in Kerala with an age shift to older children and adults. Cohorts of unimmunised, partially immunised and those with waning immunity are more at risk. The age shift observed in the current outbreak in Kerala and outbreaks in other states of India call for an urgent update in vaccination policy. In order to protect the adolescent population, the introduction of diphtheria toxoid during adolescence is essential to prevent re-emergence of diphtheria in future. Till then booster vaccination with Td at college entry may also be considered. Strategies to identify areas of low immunization coverage in addition to maintaining high routine immunization coverage is essential to maintain high herd immunity and prevention of outbreaks among children.

ACKNOWLEDGEMENTS

We acknowledge the help of the Department of Microbiology, GMC Kozhikode for laboratory support and the cooperation of Dr Sheela Mathew, Professor Infectious diseases and Dr Sindhu TG, Associate Professor in charge of Pediatric Infectious diseases Department, GMC Kozhikode for their valuable comments. We also are indebted to the Department of Health Services Malappuram and Kozhikode Districts for their support in surveillance activities.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Chandran P, Lilabi MP, Bina T, Thavody J, George S. Re-emergence of diphtheria in Kerala: the need for change in vaccination policy. *Int J Community Med Public Health* 2019;6:829-35.