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RESEARCH ARTICLE

Diphtheria Outbreak among Children in 2017–2018: a Single Centre Study in Indonesia

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Abstract

Diphtheria is an acute infectious disease caused by the bacterium *Corynebacterium diphtheriae*. Accurate and prompt diagnosis is essential for effective case management, predicting disease prognosis, preventing complications, and ensuring cost-effective medical intervention. This study aimed to assess the variety of clinical symptoms exhibited by pediatric diphtheria cases during an outbreak. An observational cross-sectional study was conducted using data from the medical records of pediatric diphtheria cases at Sulianti Saroso Infectious Disease Hospital from November 1, 2017, to February 28, 2018. The study involved 202 cases, and statistical analysis was performed using the chi-square test. Out of the 202 cases, 58.4% were male. Age distribution was <1 year: 7.4%, 1–2 years: 3.5%, >2–5 years: 24.8%, >5–12 years: 45.5%, and >12 years: 18.8%. Anamnestic findings revealed the presence of fever in 88.1% of patients, pain upon swallowing in 73.3%, and cough in 55.4%. Clinically, every patient exhibited pseudomembrane formations. Other findings included bilateral tonsillar involvement in 53%, lymphadenopathy in 40.1%, bullneck in 17.8%, and snoring in 7.9%. Four significant variables were associated with the diphtheria diagnosis: fever, snoring, bullneck, and snoring ($p<0.05$) respectively. Clinical signs and symptoms are pivotal in establishing a diphtheria diagnosis in pediatric cases.

Keywords: Children, diphtheria, outbreak

Introduction

Diphtheria is an acute disease primarily affecting the upper respiratory tract, instigated by the bacterium *Corynebacterium diphtheriae*. Remarkably, this bacterium can subsist in dust or the ambient air for durations extending to six months, enabling its propagation via droplets or direct contact.[1,2] Clinical manifestations typically encompass fever, malaise, cough, and painful swallowing. A prominent clinical feature observed upon examination is the formation of a pseudomembrane.[3,4] The criticality of laboratory investigations, such as culture or polymerase chain reaction (PCR), cannot be understated, as they detect the toxic strains that not only assail the respiratory tract, skin, and eyes but can also remain as asymptomatic carriers.[5,6] Alarmingly, toxins from 54 out of the 57 identified bacterial strains mandate prompt diagnostic and laboratory interventions to stave off dire outcomes such as cardiac failures or even sudden death.[5,7,8]

According to the World Health Organization (WHO) data, Indonesia ranks second globally, only surpassed by India, in the number of diphtheria cases and is the frontrunner amongst ASEAN countries.[9,10] 2011, there were 806 reported cases, yielding a case fatality rate (CFR) of 4.71%. In the subsequent year we showed up to 1,192 cases, with a CFR pegged at 6.38%. However, 2013 marked a reduction with 778 cases and a CFR of 5.01%. In 2017, diphtheria outbreaks spanned 170 districts/cities across 30 provinces, accounting for 954 cases and 44 deaths. The data from the onset of 2018 until January 9 indicates 14 cases spread across 11 regencies/cities in four provinces (DKI Jakarta, Banten, West Java, and Lampung), with zero mortality. The Sulianti Saroso Infectious Disease Hospital's inpatient data over the previous three years suggests a rising trend in diphtheria cases.[11,12]

Although all strains of *C. diphtheria* can instigate both endemic and epidemic diphtheria, the mitis strains typically demonstrate reduced toxicity and result in milder symptomatic presentations. Genesis of diphtheria symptoms

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can be attributed to localized inflammation of the skin or airways coupled with the systemic ramifications of exotoxins. These toxins instigate the formation of pseudomembranes—a conglomerate of fibrin, leukocytes, erythrocytes, epithelial cells, and the causative organisms—which adhere tenaciously to the underlying tissues. The ensuing pseudomembranes and concomitant tissue edema can potentially lead to airway obstructions. Toxins disseminating within the body can compromise various organs, with the heart, nerves, and kidneys particularly vulnerable. The toxin's synthesis is contingent upon lysogenic bacteriophages that house the genes responsible for the toxin's encoding. This toxin comprises three domains: one within fragment A, the catalyst unit, and two within fragment B, designated for receptor binding and insertion. Intracellularly active, the toxin precipitates cellular death.[13] Initial diphtheria presentations are typically ambiguous, marked by symptoms such as low-grade fevers, vomiting, coughs, and sore throats. Physical examinations may reveal cervical lymphadenopathy and pharyngeal erythema, which can evolve into a grayish-white exudate before culminating in pseudomembrane formation. A hallmark sign is the pseudomembrane's dirty, grayish-white appearance, which can lead to blockages due to inflamed tonsils, extending to adjacent structures, presenting the "bull neck" appearance. Dislodging these membranes is challenging, often accompanied by bleeding.[2,14]

Rapid diagnosis should be immediately based on clinical symptoms and laboratory (culture or PCR) for early treatment. The treatment used a specific antitoxin and antibiotic. The variety of symptoms that appear varies and sometimes is not typical. Pseudomembranes, as the primary symptom, can be small and do not bleed easily but give the results of culture and elective tests as toxigenic diphtheria. The discrepancy between the patient's clinical theory and therapy causes information about the clinical symptoms of diphtheria, which still needs to be improved and results in optimal case management. Therefore, this study aims to evaluate the diversity of clinical signs of diphtheria cases in pediatrics found during outbreaks.

Methods

This research is an observational study with a cross-sectional study design. The data was taken from patients' medical records diagnosed with diphtheria and diphtheria suspects from November 1, 2017, to February 28, 2018, at Sulianti Saroso Infectious Disease Hospital, which is a reference hospital for new emerging diseases in Indonesia.

Based on WHO guidelines, the clinical case definition in diphtheria is laryngitis, pharyngitis, or tonsillitis with pseudomembranes in the tonsils, pharynx, and nose. Isolation of *C. diphtheriae* from throat swabs is a laboratory diagnostic criterion.[8] The diagnosis of diphtheria is based on history, physical examination, and investigations. Based on the 2017 WHO guidelines explain that the diagnostic criteria for probable diphtheria include laryngitis, pharyngitis, tonsillitis, membranes in the nose, tonsils, and larynx or severe lymphadenopathy. A supporting examination of electrification and culture supports a confirmed diagnosis. The criteria for diphtheria for surveillance purposes are divided into suspect, probable, and confirmed diagnoses. Determination of early diagnosis is needed to determine the accuracy and speed of case management, disease prognosis, and prevent complications and other benefits, namely so that the costs incurred are practical and efficient.11 Patients with suspected diphtheria should receive anti-diphtheria serum (ADS) and antibiotics at treatment. The determination of the provision of ADS is based on the history and clinical symptoms reported by the doctor in charge of service (DPJP) to a team of experts appointed by the Ministry of Health. This study recorded as many as 202 medical records of patients who met the criteria and were diagnosed with suspected diphtheria from November 1, 2017, to February 28, 2018, meeting the ICD 10 criteria (A36, A36.0, A36.1, A36.2, A36.3, A36.8, A36.9).

The diagnosis of diphtheria is made clinically based on history, physical examination, and culture results. Inclusion criteria were pediatric patients <18 years diagnosed with suspected diphtheria, clinical diphtheria, or confirmed diphtheria. The sample size in this study was 202 samples. After the analysis, the power study was 71.70%, with a 95% confidence interval.

This study uses a questionnaire to record the data in the case medical records. The research questionnaire consisted of 3 parts: the anamnesis results, clinical symptoms, and signs. Questions about anamnesis data included age, gender,

education, place of residence, length of illness before hospital admission, immunization history, and contact history. Furthermore, questions about symptoms include weight, low fever, sore throat, runny nose, cough, hoarseness, snoring, nausea and vomiting, chest pain, shortness of breath, and palpitations. Clinical signs studied in this questionnaire such as temperature, pseudo membrane, membrane location, concha hyperemesis, pharyngeal hyperemesis, tonsil hypertrophy, lymphadenopathy, site of lymphadenopathy, "bull neck", snore, heart murmur, dysrhythmia, tachycardia, bradycardia, distant heart sounds. The researcher and the team recorded all the information needed in the questionnaire. They validated the answers in the medical record through the doctor or nurse on duty for the case. This study uses simple data analysis such as frequency and proportion to describe the patient's clinical condition, clinical signs, and demographic characteristics. The chi-square test determines the factors associated with clinical symptoms of diphtheria cases. This study received an ethical review (exempt) from the Health Research Ethics Committee of the Sulianti Saroso Infectious Disease Hospital Number 26/XXXVIII.10/VII/2018.

Results

This study involved as many as 202 (60%) respondents of child diphtheria in the period (November 2017–February 2018) diphtheria outbreaks in Indonesia in 2018 from a total of 337 cases in 2016–2018 (Figure). A total of 126 (63.4%) patients were diagnosed with clinical siphtheria, 12 (5.9%) were confirmed diphtheria patients, and 64 (30.7%) were non-diphtheria patients. In the period of diphtheria outbreaks, most cases were dominated by males, with 118 cases (58.4%) and 84 (41.6%) female cases. Table 1 shows that more than half of the respondents were from DKI Jakarta (58.9%). Most of the 87 (69.0%) clinical diphtheria patients came to the hospital three days after feeling sick symptoms—likewise, 9 (75.0%) patients with confirmed diphtheria. Most of the data/information regarding the contact history of patients with diphtheria before illness, 109 (86.5%) clinical diphtheria patients and 9 (75.0%) confirmed diphtheria patients.

Table 2 showed that most patients aged <1 year received complete immunizations according to age, namely 7 (46.7%) patients. Of 7 patients aged 1–2 years, most of them received complete immunizations 3 (42.8%); from 50 patients aged >2, Most of those five years old received incomplete immunization, namely 61 (66.3%), and of 38 patients aged >12 years, most of them received incomplete vaccination, 22 (57.9%). Table 3 showed a relationship between fever symptoms and the diagnosis of diphtheria (p=0.040). Meanwhile, there was no relationship between symptoms of shortness of breath, chest pain, and a diagnosis of diphtheria (p=0.565; 1,000, respectively). Sign of suspected diphtheria

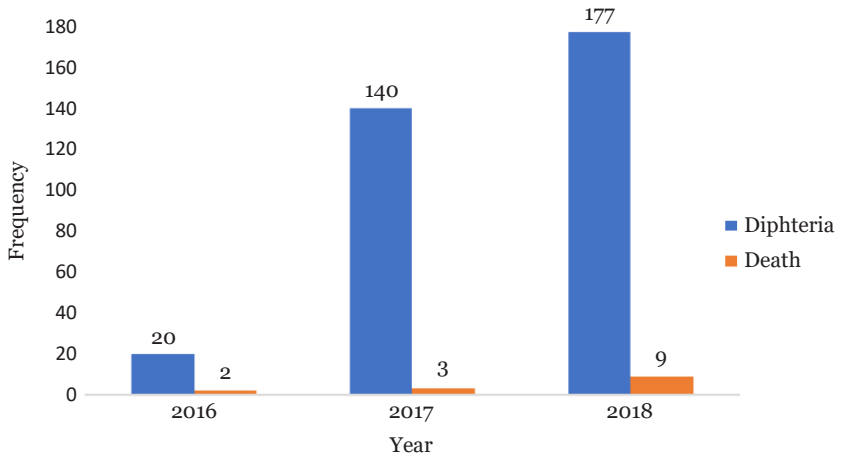

Figure Diphtheria Outbreak among Children Patients in 2016–2018 at Sulianti Saroso Infectious Disease Hospital

Table 1 Characteristics of Suspect Diphtheria Children

Variables	Suspect Diphtheria			Non-diphtheria n=64 (%)
	Clinical Diphtheria n=126 (%)	Confirm n=12 (%)	Total n=202 (%)	
Demographic				
Sex				
Male	76 (60.3)	4 (33.3)	118 (58.4)	38 (59.4)
Female	50 (39.7)	8 (66.7)	84 (41.6)	26 (40.6)
Domicile				
DKI Jakarta	72 (57.1)	8 (66.7)	119 (58.9)	39 (60.9)
Outside DKI Jakarta	54 (42.9)	4 (33.3)	83 (41.1)	25 (39.1)
History of contact				
Yes	1 (0.8)	0 (0)	5 (2.5)	4 (6.2)
No	125 (99.2)	12 (100)	197 (97.5)	60 (93.8)
Clinical onset (days)				
<3	39 (31.0)	3 (25.0)	66 (32.7)	24 (37.5)
≥3	87 (69,0)	9 (75.0)	136 (67.3)	40 (62.5)

Table 2 History of Vaccination of Suspected Diphtheria Cases

Age (Years)	History of Vaccination			
	Unvaccinated Children n=9 (%)	No Data n=42 (%)	Fully Vaccinated Children based on Age n=35 (%)	Partially Vaccinated Children n=116 (%)
<1	2 (13.3)	2 (13.3)	7 (46.7)	4 (26.7)
1–2	1 (14.3)	2 (28.6)	3 (42.8)	1 (14.3)
>2–5	3 (6.0)	10 (20.0)	9 (18.0)	28 (56.0)
>5–12	3 (3.3)	14 (15.2)	14 (15.2)	61 (66.3)
>12	0 (0)	14 (36.8)	2 (5.3)	22 (57.9)

in children is shown in Table 4. There was a relationship between the "bull neck", snore, and the diagnosis of diphtheria (p=0.011; 0.023, respectively).

Discussion

This study showed that among the 202 cases, 5–12 years were the most common age group, namely 92 (45.5%) patients. Patients aged 5–12 years with clinical diphtheria were 46.8%, and 58.3% with confirmed diphtheria. A study in Delhi found a similar picture, with 93% of patients aged less than nine years.[15,16] Meanwhile, reports on outbreaks of research in the USA and ex-Soviet countries found an epidemiological shift in the age of diphtheria sufferers from pre-school age to school age and adulthood which illustrates the low level of antibodies in this age group, so that during outbreaks, this group becomes susceptible to diphtheria.[17] In contrast to the study in Surabaya, which stated that most diphtheria patients were under the age of 5 years, namely 61.5%, followed by ages 5–10 years, as many as 31.8% and the rest at the age of more than ten years.[18] Regarding domicile, most clinical and confirmed diphtheria patients reside in Jakarta, while those outside Jakarta are satellite cities of the capital city (Bekasi, Depok, Bogor, and Tangerang).

Most patients aged 2–5 years, >5–12 years, and >12 years had incomplete immunization status. This case of no data could be caused by not being asked in the anamnesis or not remembering the child's immunization history. Incomplete immunization is generally due to not repeating immunization after 12 months of age. DPT repeat immunization only entered the national program in 2014, so most patients over the age of 5 years will have incomplete immunizations if they are

Table 3 Symptoms of Suspected Diphtheria in Children

Variables	Diagnosis		Total n=202 (%)	p	OR (95% CI)
	Diphtheria* n=138 (%)	Non-diphtheria n=64 (%)			
Fever					
Yes	126 (70.8)	52 (29.2)	178 (100)	0.040**	2.42 (1.02–5.74)
No	12 (50.0)	12 (50.0)	24 (100)		
Painful swallow					
Yes	106 (71.6)	42 (28.2)	148 (100)	0.095	1.74 (0.91–3.32)
No	32 (59.3)	22 (40.7)	54 (100)		
Dysfagia					
Yes	38 (73.1)	14 (26.9)	52 (100)	0.392	1.36 (0.67–2.73)
No	100 (66.7)	50 (33.3)	150 (100)		
Rhinopharyngitis					
Yes	46 (65.7)	24 (34.3)	70 (100)	0.563	0.83 (0.45–1.55)
No	92 (69.7)	40 (30.3)	132 (100)		
Cough					
Yes	82 (73.2)	30 (26.8)	112 (100)	0.095	1.66 (0.91–3.02)
No	56 (62.2)	34 (37.8)	90 (100)		
Hoarse					
Yes	5 (55.6)	4 (44.4)	9 (100)	0.468[a]	0.56 (0.15–2.17)
No	133 (68.9)	60 (31.1)	193 (100)		
Dyspnea					
Yes	9 (60.0)	6 (40.0)	15 (100)	0.565[a]	0.67 (0.23–1.98)
No	129 (69.0)	58 (31.0)	187 (100)		
Chest pain					
Yes	3 (75.0)	1 (25.0)	4 (100)	1.000[a]	–
No	135 (68.2)	63 (31.8)	198 (100)		
Pounding chest					
Yes	1 (100)	0 (0)	1 (100)	1.000[a]	–
No	137 (68.2)	64 (31.8)	201 (100)		
Nausea/vomiting					
Yes	19 (70.4)	8 (29.6)	27 (100)	0.805	1.12 (0.46–2.71)
No	119 (68.0)	56 (32.0)	175 (100)		

Note: *clinical diphtheria and confirm cases, **p<0.05 significant, [a]Fisher's exact

Table 4 Signs of Suspected Diphtheria in Children

Variables	Diagnosis		Total n=202 (%)	p	OR (95% CI)
	Diphtheria* n=138 (%)	Non-diphtheria n=64 (%)			
Lymphadenopathy					
Yes	60 (74.1)	21 (25.9)	81 (100)	0.150	1.57 (0.85–2.93)
No	78 (64.5)	43 (35.5)	121 (100)		
Bullneck					
Yes	31 (86.1)	5 (13.9)	36 (100)	0.011**	3.42 (1.26–9.26)
No	107 (64.5)	59 (35.5)	166 (100)		
Snore					
Yes	15 (93.8)	1 (6.3)	16 (100)	0.023**	7.68 (0.99–59.49)
No	123 (66.1)	63 (33.9)	186 (100)		

Note: *clinical diphtheria and confirm cases, **p<0.05 significant

immunized at *posyandu*, *puskesmas*, or schools.

These results are similar to the diphtheria outbreak in Kolkata, India. Outbreaks caused by low immunization coverage at age replicates.[19,20] A history of contact with diphtheria sufferers was experienced in 2% of cases. This may be because most diphtheria carriers are asymptomatic.[21] In fact, these data are needed to support the diagnosis of patients. All household contacts or people who have had contact with diphtheria patients should be monitored closely during the incubation period, which is seven days.[22,23] Diphtheria can be prevented by immunization, and immunization has been a national program since 1976.[24] Diphtheria immunization is given five times between the ages of 6 weeks to 6 years: 3 times before the period of 12 months as a basic immunization and repeated at the age of 18–24 months, and 5–6 years after that every ten years. The coverage of DPT basic immunization in Jakarta based on *Riskesdas* 2013 is 79.1%. The highest is between Banten (63.3%) and West Java (71.5%) which are directly adjacent.[25]

The interval between the clinical onset and hospitalization was ≥3 days in both clinical diphtheria and confirmed diphtheria cases. Most of the data are unavailable in clinical and confirmed cases of diphtheria. This may be because most diphtheria carriers are asymptomatic,[20–22,26] so patients do not realize that people around them can transmit these germs. However, the data is essential to support the diagnosis of patients.

The anamnesis results showed that the most common patient complaint was fever, which was significantly associated with the diagnosis of diphtheria ($p<0.05$). As with a study in Andhra Pradesh, India, Meera found all patients diagnosed with diphtheria complained of fever. Most diphtheria patients feel pain when swallowing.[27–29] Sore throat, runny nose, hoarseness, shortness of breath, chest pain, palpitations, nausea, and vomiting are rarely found in cases of diphtheria. In contrast to a study in Andhra Pradesh, India Meera, most diphtheria patients experience sore throat, runny nose, nausea, and vomiting.[28] These symptoms are not specific because they are also found in non-diphtheria disease. Test results ($p>0.05$). In contrast to cough, which diphtheria patients mostly feel. The chi-square test results showed that the results were insignificant ($p>0.05$). However, these symptoms are variations that each diphtheria patient feels.

Clinical signs found that all patients suspected of diphtheria had pseudomembranes. It was found in all diphtheria patients, with the most locations in the tonsils. Bleeding membranes were only found in 6 cases, in contrast to the basic concept that pseudomembranes in diphtheria bleed easily. As many as 18.8% of cases also showed the form of a membrane in the form of detritus, not thick plaque. It may be due to the early phase of the disease. Three out of 18.8% cases with detritus membrane form also gave confirmatory results for diphtheria examination, so caution must be exercised in diagnosing diphtheria based on the membrane shape.[30]

Lymphadenopathy is found in most diphtheria patients, while there was no relationship between lymphadenopathy and the diagnosis of diphtheria ($p>0.05$). "Bull neck" and snore are primarily found in diphtheria patients. "Bull neck" is one of the complications of diphtheria, so these symptoms can help establish a clinical diagnosis.[28,31,32] The same applies to snore, which occurs due to the "bull neck" experienced by diphtheria patients. The chi-square test results obtained $p<0.05$, so it can be concluded that "bull neck" or snore patients as symptoms of diphtheria. Research in Andhra Pradesh, India Meera, proved that most "bull necks" were found in patients diagnosed with diphtheria.[28] Meanwhile, snore was only found in patients diagnosed with diphtheria. Soft tissue edema (pseudomembrane) and enlarged lymph nodes (lymphadenopathy) can cause a "bull neck." This condition will block the airway, which is characterized by the presence of snore.[5,15]

Conclusions

Diphtheria in pediatric patients often presents with fever as a notable symptom. Furthermore, complications such as "bull neck" and snore are significant indicators and are closely linked to the diagnosis of diphtheria. These clinical manifestations can aid healthcare professionals in promptly identifying and managing diphtheria cases, especially during outbreaks. Recognizing these symptoms early on is crucial for timely intervention and reducing potential complications associated with this infectious disease.

Conflict of Interest

We declare no conflict of interest in this study.

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