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**Case Series: Confirmed Diphtheria at Sulianti Saroso Infection Center Hospital in The Post-pandemic Period**

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**Abstract**

**Background:** Diphtheria vaccine coverage decreased during the Covid-19 pandemic. Diphtheria is caused by *Corynebacterium diphtheria*, which infects the upper respiratory system and produces toxins circulating in the body. The disease was fatal, with a mortality rate higher in children. This study described a case series of confirmed hospitalised diphtheria patients at Sulianti Saroso Infectious Disease Hospital (SSIDH) eighteen months post-pandemic. **Objective:** to describe epidemiological characteristics, laboratory examinations and outcomes of hospitalised diphtheria patients at SSIDH from January 1st, 2022, to June 31<sup>st</sup>, 2023. **Case Presentation:** We reported ten confirmed diphtheria cases based on RT-PCR and clinical and epidemiological diagnosis. Of the ten cases, nine were children (<18 years old), six were male patients, and five lived in Jakarta. Based on Albert staining, 9 of 10 samples were found to be bacilli, positive-gram bacteria with metachromatic granular. **Result:** According to the RT-PCR examination, eight cases were confirmed positive for toxigenic diphtheria, five were a mitis subtype, one was a gravis subtype, and the other four were undetected. Based on clinical examination, eight cases were classified as severe diphtheria, five cases included myocarditis, and three patients passed away. Pediatric cases dominated diphtheria cases. RT-PCR examinations are more accurate and specific to finding toxigenic subtypes in the Jakarta Metropolitan Area. **Conclusion:** The detection of diphtheria cases in adult's highlights concerns about adult immunity and awareness of vaccination. Vaccination campaigns and booster shots are essential, alongside continuous surveillance and accurate testing to prevent a resurgence of the disease.

**Keywords:** case series, diphtheria, toxigenic

**Case Report**

**INTRODUCTION**

Diphtheria is a highly contagious illness caused by *Corynebacterium diphtheria*. It primarily affects the upper respiratory system, producing toxins that can cause severe damage to other organs. The disease spreads through direct physical contact or inhaling droplets from the cough or sneeze of an infected person. Diphtheria remains a potentially fatal disease, particularly in children with a mortality rate

ranging from 5-10% and even higher in certain regions where proper diagnosis and treatment are lacking, reaching 50%. Vaccination has significantly decreased the incidence of diphtheria-related deaths and illnesses. However, it remains a significant health concern in countries with low vaccination coverage (Metcalf, 2020). Even though diphtheria is a preventable disease, its low vaccination coverage during the pandemic caused the disease to be widely spread in all provinces in Indonesia and has even shown an increase in morbidity and mortality rates after the COVID-19 pandemic.

Before the COVID-19 pandemic, Indonesia reported 948 cases of diphtheria in 2019. Most (81%) had not completed a full vaccination dose or had no diphtheria vaccination. In 2020, it reported diphtheria cases had decreased to 259 cases with a CFR of 5.02% (13 deaths). In 2021, diphtheria cases decreased to 235, but CFR increased significantly to 11% (25 deaths) (Metcalf, 2020; Kemenkes, 2021).

The COVID-19 pandemic has caused wide-scale disruptions impacting many essential services, including the health sector. Fear of getting infected in health facilities, the unpreparedness of healthcare facilities, and limited mobilisation affect health services, particularly the routine vaccination schedule for children. As a result, vaccination coverage and herd immunity also decrease, so the concern about outbreaks of diseases preventable by immunisation, such as diphtheria, is inevitable (Ranganathan & Khan, 2020; Indahsari, 2021) Increasing diphtheria cases should be paid attention to due to the high fatality rate, reaching up to 50% in untreated cases and null immunity and 10% in inappropriate treatment (Centers for Disease Control and Prevention, 2012)

At Sulianti Saroso Infectious Disease Hospital (SSIDH), the number of referred diphtheria cases decreased from 298 in 2018 to 189 in 2019. During the COVID-19 pandemic, SSIDH was appointed a national referral centre for COVID-19 cases, so the number of diphtheria cases has been significantly reduced. However, several diphtheria patients received treatment sequentially from 2020 to 2022: 35, 5, and 38 hospitalised diphtheria cases. After the COVID-19 pandemic status in Indonesia was lifted, SSIDH treated 27 cases of diphtheria, with one fatal case.

A study about increasing preventable infectious disease post-pandemic has not been conducted widely. This study is one of the earliest diphtheria studies held after the COVID-19 pandemic, particularly in Indonesia. The study aimed to provide an overview of epidemiological characteristics, laboratory examination results, and outcomes of confirmed cases of diphtheria hospitalised at RSPI Sulianti Saroso from January 1, 2022, to June 31, 2023. We present a series of diphtheria cases based on confirmation of Culture results and clinical and/or epidemiological diagnosis. These cases were investigated in-depth through epidemiological investigations to gather comprehensive information.

## CASE PRESENTATION

### Data Collection

Data were collected through a comprehensive review of medical records for all patients admitted to SSIDH with suspected diphtheria during the study period. The following steps were taken to ensure thorough data collection:

1. **Patient Identification:** Patients were identified through hospital admission logs and laboratory records indicating diphtheria testing.
2. **Clinical Assessment:** Each patient underwent a detailed clinical assessment, including a review of symptoms, medical history, and potential exposure to confirmed diphtheria cases.

### Patient Selection

Patients were selected based on specific criteria to ensure the relevance and accuracy of the case series:

1. **Confirmation of Culture Results:** Cases with positive cultures for *Corynebacterium diphtheriae* were included as confirmed cases.

2. **Clinical Diagnosis:** In addition to culture-confirmed cases, patients exhibiting clinical symptoms consistent with diphtheria were included, even if their culture results were negative. This was particularly relevant for cases where clinical presentation strongly indicated diphtheria.
3. **Epidemiological Link:** Patients with a documented history of close contact with confirmed diphtheria cases were also included, regardless of culture results. This criterion was crucial for understanding the transmission dynamics of the disease.

#### **Case Details**

Total Cases: 10, Confirmed Cases: 8 (based on positive culture results), Clinical/ Epidemiological Cases: 2 (selected despite negative culture results)

#### **Data Analysis**

Data analysis involved a descriptive approach, summarizing the clinical characteristics, outcomes, and epidemiological links of the cases. Statistical methods were employed to analyze the demographic data and clinical outcomes, providing insights into the severity and complications associated with diphtheria in the studied population.

Based on epidemiological characteristics, 9 cases were children, while 1 case was adult patients, consisting of 6 males and four females. Based on regional distribution, 5 cases came from Jakarta, three from Bekasi, and the rest from Bogor. We found seven patients with no history of diphtheria vaccine, and the other three had completed basic diphtheria vaccination.

Based on laboratory examination results using the Albert staining technique, 9 cases showed gram-positive bacilli with metachromatic granules. PCR examination confirmed 8 cases as positive for toxigenic diphtheria, while 2 cases were negative. Among the subtypes identified, there were 5 cases of the mitis subtype, 1 case of the gravis subtype, and 4 cases where no subtype was detected.

Antidiphtheria serum (ADS) was administered based on the severity of the cases, determined by the membrane area and the onset of illness. Eight severe cases received ADS doses ranging from 80,000 to 100,000 IU, while two moderate cases received ADS doses of 40,000 IU. Out of the 10 cases, five developed myocarditis complications. Regarding the outcomes, seven patients survived, while three unfortunately passed away.

**Table 1.** Distribution of cases based on demographics, vaccination history, laboratory tests, ADS administration, complications and case outcomes

Cases	Age (years)	Gender	Domicile	Basic Vaccination	Metachromatic Granule	Culture result	Subtype	RT-PCR	ADS treatment (IU)	Complication	Survival
01 (AA)	2	Male	West Jakarta	Yes	Yes	Positive	N/A	Toxigenic	40.000	-	Survive
02 (NA)	3	Female	Bogor Regency	No	No	Positive	Mitis	Toxigenic	80.000	-	Survive
03 (RFZ)	3	Male	Bekasi City	No	Yes	Positive	Mitis	Toxigenic	80.000	-	Survive
04 (ASP)	4	Male	East Jakarta	No	Yes	Positive	Mitis	Toxigenic	80.000	Myocarditis	Not survive
05 (RA)	4	Male	East Jakarta	Yes	Yes	Negative	N/A	N/A	40.000	-	Survive
06 (PSR)	5	Female	South Jakarta	No	Yes	Negative	N/A	N/A	80.000	Myocarditis	Not survive
07 (SA)	7	Female	Bekasi Regency	Yes	Yes	Positive	Mitis	Toxigenic	100.000	Myocarditis	Survive
08 (KAN)	7	Female	Bogor Regency	No	Yes	Positive	N/A	Toxigenic	80.000	Sepsis, Myocarditis	Not survive
09 (ISS)	8	Male	Bekasi Regency	No	Yes	Positive	Gravis	Toxigenic	100.000	Myocarditis	Survive
10 (MI)	33	Male	North Jakarta	No	Yes	Positive	Mitis	Toxigenic	80.000	-	Survive

N/A = Not Available

## DISCUSSION

The outbreak of diphtheria was influenced by the COVID-19 pandemic, where access to vaccination services is limited due to restrictions on mobility. As the pandemic transitions to an endemic state, community activities gradually resume, increasing transmission and rising mobility. Additionally, the presence of asymptomatic carriers of diphtheria, who unknowingly transmit the disease, further contributes to case numbers. Children, being a vulnerable demographic, are particularly susceptible to exposure, making them the most affected age group.

Immunity to *Corynebacterium diphtheriae* declines progressively with age, as stated in the Morbidity and Mortality Weekly Report (MMWR) by the Centers for Disease Control and Prevention (CDC), from 91% at the age of 6-11 years decreases to 80% at adolescence and to about 30% at the age of 60-69 years. Therefore, to prevent the incidence of diphtheria, the United States Advisory Committee on Immunization Practices recommends routine vaccination for all age groups, including adults and healthcare workers (Liang et al., 2018).

Based on immunisation status, out of the six children aged five years or younger, four had not received immunisations. These four cases experienced severe diphtheria, with two resulting in death. The other two children, who had received the basic diphtheria immunisation, survived and recovered. There were three cases of children who were 6-12 years old. Two of them had never received basic immunisations, while they should have received a diphtheria booster, both DT and Td, at school. Epidemiological investigations revealed that none of these children had received booster immunisations at school. The COVID-19 pandemic led to declining vaccination coverage, affecting basic and booster vaccine programs. Implementing distance learning in school also disrupted the booster programs (Indahsari, 2021). Healthcare providers should prioritize education on the importance of vaccination and actively engage with communities to address concerns. Public health policies should be based on the data, emphasizing the need for targeted interventions in high-risk areas. Prameswari and Retnaningsih found that family size, attitude, and interpersonal reference group were significantly associated with conformity of the diphtheria immunization schedule. They also added that maternal higher education and family monthly per capita income are related to schedule conformity (Prameswari & Retnaningsih, 2023).

However, despite the pandemic, awareness of the importance of immunisation for children is needed. The pandemic situation is not a reason not to vaccinate children. In this series of cases, most children have never received basic vaccines and have an uncompleted history of diphtheria vaccine. This indicates that even before the pandemic, some parents did not understand the importance of immunisation. Further investigation revealed that some parents refused immunisation due to their beliefs and lack of awareness about its significance.

The cases were spread from Jakarta's various areas, including its satellite cities, such as Bekasi and Bogor, which are high-population areas. Some studies suggest that individuals living in densely populated areas are more likely to come into close contact with others, leading to the rapid spread of infectious diseases. However, population density alone does not necessarily determine the ease of infection spread within a population. Other factors, such as social habits, education levels, occupation, vaccination status, and various other factors, also play significant roles in the transmission of diseases. (Solomon, 2023).

The ability of *Corynebacterium diphtheriae* to produce diphtheria toxin can be classified into two types: toxigenic and non-toxigenic (Maemun et al., 2022; Prygiel et al., 2022). The toxigenic type can produce toxins and has the potential to be fatal to humans. When these bacteria enter the body, they release toxins that spread through the bloodstream and cause tissue damage. The toxin attacks specific nerves, particularly in the throat, leading to difficulty swallowing within the first week. The damage from diphtheria toxin can be severe, potentially resulting in heart failure and sudden death (Hoefer et al., 2021).

Since *C. diphtheriae* infection requires immediate treatment due to its potential to be life-threatening, laboratory tests are essential for confirming the diagnosis, classifying diphtheria cases, and determining the subtype or variant of *C. diphtheriae*. The gold standard for diphtheria laboratory examination is culture, with toxicity detection determined by the ELEK test or PCR. However, because culture examination takes a considerable amount of time and can only be performed in reference laboratories, initial examinations can employ Albert or Neisser's staining techniques as alternatives to support the early diagnosis of diphtheria (Kemenkes RI, 2018; World Health Organization, 2024; Rosana et al., 2020).

We conducted a microbiological examination with Albert staining as an early diagnosis. The specimens were referred to the Center for Environmental Health Engineering and Disease Control for PCR and culture examination. Based on Albert's staining, nine samples contained metachromatic granules, while according to the culture results, eight positive cases of toxigenic strain *C. diphtheriae* were found. Several studies compared Albert's staining with the PCR method. Although microscopic smear examination is low-cost, quick, and easy, the sensitivity and specificity are poor. A 2023 study from SSIDH reported that Albert's staining has a low sensitivity of 31.81% but a high specificity of 82.60%, with a positive predictive value of 36.84% and a negative predictive value of 79.16%. This indicates that Albert's staining is better at detecting negative results than positive ones. Therefore, this method does not meet the diagnostic requirements, which demand sensitivity and specificity above 80% (Fauzi, 2023).

In this study, 8 cases obtained positive and two negative culture results. Negative culture results could be influenced by various factors, including the procedures followed by personnel and specimen management methods. The principle of successful bacteriological examination is determined from the technique of specimen collection, use of transport media, storage and delivery of specimens, and the proficiency of laboratory personnel. Specimen collection should be done before antibiotic administration to prevent false negatives. Collecting specimens from pediatric patients is generally more challenging than from adults, as uncooperative patients can lead to inadequate sampling and negatively affect test results. Therefore, in addition to PCR examination of culture isolates, PCR testing on clinical specimens should also be performed to increase the positive detection rate of culture results potentially.

The administration of antitoxins in treating diphtheria depends on the disease severity and does not distinguish the dose in children and adults. In this study, most patients underwent a severe stage of diphtheria due to either extensive pseudomembrane area, bull neck or myocarditis. Severe diphtheria, with or without complications and a history of delayed treatment, is further exacerbated by inadequate vaccination. Most patients were referred after visiting multiple health facilities before reaching SSIDH, indicating a significant delay from the onset of symptoms to receiving appropriate diphtheria treatment. This delay also contributes to the severity of the patient's condition. They were given 80,000 IU of ADS in 6 cases and 100,000 IU in 2 cases. Of the 8 cases of severe diphtheria, 5 cases experienced myocarditis, and 3 of them didn't survive. A study conducted in India mentioned delayed administration of anti-diphtheritic serum ( $\geq 5$  days) significantly contributed to complications and mortality in diphtheria cases. The study emphasized that timely treatment within 72 hours reduces the risk of neurological complications and improves outcomes in affected children (Pooja & Yadav, 2025). Another study in Bangladesh shown that delayed DAT administration is associated with higher mortality rates and severe complications. In a retrospective study of diphtheria patients treated with DAT, those who received timely treatment had a recovery rate of 98%, while delays in administration were linked to adverse outcomes (Eisenberg et al., 2021).

The cornerstone of managing diphtheria is the timely administration of antibiotics and DAT in order to reduce morbidity and mortality. Drugs that are known to improve favourable illness outcomes, such as intravenous erythromycin and DAT, are now not easily accessible (Medugu et al., 2023). When given within 48 hours of the disease's commencement, diphtheria antitoxin (DAT) has been shown to enhance disease outcomes. Serious side effects that could be fatal are linked to

delaying the administration of DAT and not using intravenous erythromycin or other efficient antibiotics to remove the pathogenic organism. According to this study, the death rate increases by 100% for every 24-hour wait. The severity of the disease determines the dosage of DAT, which only neutralises circulating toxins before they are bound to the tissues (Denue et al., 2024).

Death from diphtheria is usually caused by toxin-mediated myocarditis. A study that investigated diphtheria outbreaks in Jakarta and Tangerang in 2018 stated that myocarditis complications occurred in 45 patients out of a total of 283 patients (15.9%), and 10 of them died. Myocarditis was present in all fatal cases ( $p < 0.001$ ) and associated with a mortality rate of 60-70% of cases, making it the leading cause of death in diphtheria infection. A prospective study in Vietnam reported that 40% of patients with myocarditis showed symptoms of cardiomyopathy on the day they were hospitalised (Chanh et al., 2022). The rest of the patients who were initially asymptomatic were later diagnosed with cardiomyopathy during their treatment. Twelve patients out of a total of 32 patients (37.5%) with cardiomyopathy did not survive (Arguni et al., 2021). About 10–25% of individuals with respiratory diphtheria have cardiac problems, particularly myocarditis. With a 50–75% mortality rate, cardiac involvement is the most common cause of diphtheria-related deaths (Ilyas et al., 2024).

The main cause of death from diphtheria is myocarditis. The most severe type of diphtheria and the leading cause of death for these patients is cardiac involvement, specifically myocarditis (Arvind et al., 2022). Although early DAT delivery is essential, its efficacy decreases as soon as the diphtheria toxin attaches to tissues, and its restricted manufacturing may make it difficult to obtain globally. The use of mechanical circulatory support, particularly with left cavity drainage systems, can be crucial in cases of refractory cardiogenic shock (Esmel-Vilomara et al., 2025; Sharma et al., 2019; Lamichhane & Radhakrishnan, 2024).

A thorough examination of the study's limitations is necessary to contextualize the findings. Data collection was challenging as our hospital is a tertiary hospital. We believed many simpler diphtheria cases had been handled in the primary and secondary hospitals. The small sample size may limit the generalizability of the results, and potential selection bias could skew the data. Acknowledging these limitations strengthens the study's credibility and highlights areas for improvement in future research. Future studies should aim for larger, more representative samples to enhance the reliability of the findings.

## CONCLUSION

This study indicates that children continue to represent the majority of diphtheria cases. However, the detection of diphtheria in adults should alert clinicians and epidemiologists to the issue of low immunity among adults, the increased mobility post-pandemic, and the low parental awareness about the importance of vaccination could lead to a resurgence of this severe and potentially fatal disease. Consequently, conducting vaccination campaigns for children and administering diphtheria booster shots for adults remains crucial. PCR testing provides more accurate and specific results than Albert's staining, enabling the identification of the diphtheria subtypes producing toxigenic strains in the Jakarta Greater Area. This highlighted the necessity for continuous epidemiological surveillance, ensuring early detection of diphtheria cases, and assessing the effectiveness of the vaccination program.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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