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Original Article

# Correlation between immunization status and pediatric diphtheria patients outcomes in the Sampang District, 2011-2015

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## Abstract

***Background*** The number of diphtheria cases recently increased, such that an outbreak was declared in East Java Province, which includes the Sampang District. Immunization completion status is a determining factor for diptheria infection.

***Objective*** To investigate for correlations between immunization status and outcomes (severity level, fatality, and complications) of diphtheria patients in the Sampang District.

***Methods*** This analytic, cross-sectional study used secondary data from the East Java Provincial Health Office on diphteria patients aged 0-20 years during the 2011-2015 outbreak in the Sampang District and interviews with diphtheria patients in that region. *The Diphtheria Research Team* of Dr. Soetomo Hospital collected data on immunization status, diphtheria severity (mild, moderate, or severe), case fatality (died or survived), and complications in the patients (with or without complications). Spearman's, Chi-square, and Fisher's exact tests were used for data analyses, accordingly.

***Results*** Seventy-one patients with clinical diphtheria were identified, 17 of whom were confirmed with positive culture results. The case fatality rates were 7% in patients with clinical and 5.9% in confirmed diphtheria. There were no correlations between patient immunization status and severity (P=0.469 clinical, P=0.610 confirmed), or fatality (P=0.618 clinical, P=0.294 confirmed) of diphtheria in the clinical and confirmed diphtheria patients. However, there was a correlation between patient immunization status and the emergence of complications in clinical (P=0.013), but not in confirmed (P=0.620) diphtheria patients.

***Conclusion*** There is a correlation between immunization status and complications in clinical diphtheria patients. Such a correlation is not found in confirmed diphtheria cases because none of the patients had complete immunization status. **[Paediatr Indones. 2018;58:110-15; doi: http://dx.doi.org/10.14238/pi58.3.2018.110-15]**.

***Keywords:*** *diphtheria; immunization status; diphtheria severity; fatality; complication*

Diphtheria is an acute infectious disease that mainly affects infants and children in the early years of life.[1] The number of diphtheria cases has decreased throughout the world. However, the East Java Provincial Government of Indonesia declared a diphtheria outbreak due to a high number of diphtheria cases in the province, including the Sampang District. From 2009 to 2012, there were approximately 1,870 reported diphtheria cases in the province, with 643 cases clinically diagnosed with diphtheria in healthcare centers. Out of 643 cases of diphtheria based on calinical diagnosis, fifty of them were confirmed by positive culture results based on official reports released between 2013 to 2014.[2,3] In the Sampang District alone, approximately 91 cases were found from 2011 to 2015.

Diphtheria is caused by the Corynebacterium diphtheria bacterial exotoxin.[1] The diphtheria toxin's main mode of action is to inhibit protein synthesis. This toxin may spread relatively quickly to different parts of

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the body, causing complications in the patients, such as myocarditis and neurologic dysfunction.[4-6] Diphtheria is transmitted mainly by droplets from sneezing and coughing, but also may be transmitted through direct contact with cutaneous diphtheria wounds.[7] Initially, the signs and symptoms of diphtheria are non-specific, such as malaise, fever around 38° Celsius, hoarseness, sore throat, and rhinorrhea. As the disease progresses, pseudomembranes develop in most cases, which may cause respiratory tract obstruction. This obstruction may lead to patient fatality.[7] A definitive diagnosis of diphtheria is carried out by obtaining specimens from suspected lesions and culturing them in media specific for Corynebacterium diphtheria.[4,6,7] Supportive examinations may also be carried out to assist the diagnostic process, in form of polymerase chain reaction (PCR), antibiotic-sensitivity test to identify antimicrobial resistance, Elek test to identify diphtheria toxin, and Shick test to identify serum antibodies against the diphtheria toxin.[8,9]

The number of diphtheria cases has been significantly reduced since the discovery and introduction of a diphtheria vaccination. Vaccine administration stimulates the production of antibodies against diphtheria toxin, mainly IgG and IgA, making the toxin unable to bind to the toxin receptor during future infection.[4] Studies have shown that of many factors affecting diphtheria spread in society, immunizations stand out as the most significant and influential factor.[10] We aimed to identify correlations between immunization status and diphtheria severity level, fatality, and complications in the Sampang District during the diphtheria outbreak from 2011 to 2015.

## Methods

This study was an analytic study with a cross-sectional approach. Subjects were patients with clinical diagnoses of diphtheria in the Sampang District of Madura Island, East Java. Data were obtained from the East Java Provincial Health Office on diphtheria patients from 2011-2015 and by interview conducted towards the patient of the 2011-2015 diphtheria outbreak in the region by the Diphtheria Research Team of Soetomo Hospital consisting of pediatrician, residents, doctors, epidemiologists, public health officers, nurses, and medical students. The inclusion criteria were patients with a clinical diagnosis of diphtheria, maximum age of 20 years at the time of diagnosis, complete data and/or medical records, and diagnosed as not immunocompromised by a medical doctor. The minimum required number of subjects was calculated using the hypothesis test formula for two samples, and found to be 56.

The independent variable in this study was the patient immunization status, which was classified as "complete," "incomplete," or "unimmunized," according to the Indonesian Ministry of Health standards.[11] The dependent variables were the degree of severity, fatality, and complications in the patients. The degree of diphtheria severity was classified according to the *2008 Diagnosis and Therapy Guidelines* of Dr. Soetomo General Hospital, Surabaya, Indonesia, into "severe," "moderate," or "mild" diphtheria. Fatality was defined as the final outcome of of death due to diphtheria. Complication was defined as the presence of bullneck, myocarditis, shock, or bleeding manifestation.[6] Spearman's, Chi-square, and Fisher's exact tests were used for statistical analyses by *SPSS Statistics 23.0* software. This study was approved by the Ethics Committee for Health Research of Airlangga University Medical School, Surabaya.

## Results

There were 81 diphtheria patients recorded in the Sampang District during 2011-2015. Ten patients were not included because of aged ≥ 20 years and/or incomplete data. Seventy-one patients with clinical diagnoses of diphtheria were included in this study, 17 (23.9%) of whom had positive culture results for Corynebacterium diphtheriae. Most of them were positive for *mitis biovar,* as described in **Table 1**.

Most diphtheria patients were female and characteristics of the patients were relatively similar between the two groups (clinical and confirmed

**Table 1**. Culture results of the subjects

| Culture results | (N=71) |
|---|---|
| Positive, n (%) | |
| Gravis biovar | 2 (2.8) |
| Mitis biovar | 15 (21.1) |
| Negative, n(%) | 54 (76.1) |

diphtheria). Both groups were predominantly aged 5-9 years at the time of infection. Both groups also had relatively similar age characteristics. But the patients with confirmed diphtheria had a slightly narrower age range at the time of infection. Subjects' characteristics are summarized in **Table 2**.

**Table 2.** Characteristics of the subjects

| Characteristics | Clinical diphtheria (n=71) | Confirmed diphtheria (N=17) |
|---|---|---|
| Sex, n (%) | | |
| Male | 29 (59.2) | 7 (41.2) |
| Female | 42 (40.8) | 10 (58.8) |
| Age group, n (%) | | |
| 0-4 years | 21 (29.6) | 4 (23.5) |
| 5-9 years | 31 (43.7) | 8 (47.1) |
| 10-19 years | 19 (26.8) | 5 (29.4) |
| Age characteristics, n (%) | | |
| Mean (SD), years | 7.19 (4.289) | 7.77 (4.2061) |
| Median, years | 6 | 7 |
| Minimum, years | 1 | 3 |
| Maximum, years | 19 | 18 |

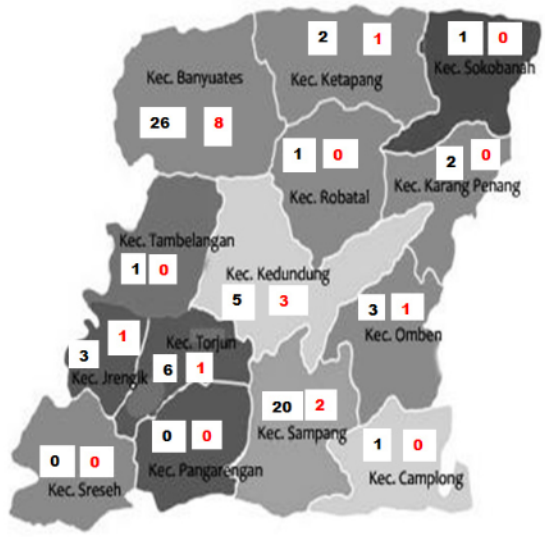


**Figure 1.** Map of diphtheria patient distribution by-district in the Sampang District. Left box (black font): number of patients with clinical diphtheria; Right box (red font): number of patients with confirmed diphtheria.

Diphtheria patients were found in 12 out of the total of 14 districts in the Sampang District. A large number of cases were found in Banyuates District and Sampang District. However, no patients were found in Sreseh and Pangarengan Districts, as shown in **Figure 1**.

There was a larger proportion of severe diptheria in patients without complete immunizations. However, Spearman's correlation test revealed no significant correlation between immunization status and the degree of diphtheria severity of in patients with clinical and confirmed diphtheria (**Table 3**).

Fisher's exact test revealed no significant correlation between immunization status and fatality status in diphtheria patients with clinical and confirmed diphtheria (**Table 4**).

Complications occurred in 26 out of 71 (36.6%) diphtheria patients. The majority of patients with complications had bullneck, as displayed in **Table 5**. From the total of 26 patients having complications of diphtheria, 8 of them belong to the group of 17 patients with confirmed diphtheria, which were analyzed further. Chi-square test revealed a significant correlation between immunization status and complications of patients with clinical diphtheria, but no correlation between immunization status and complications in patients with confirmed diphtheria (**Table 6**).

**Table 3.** Analysis of immunization status and degree of severity

| Diphtheria status | Immunization status | Diphtheria severity | | | P value |
|---|---|---|---|---|---|
| | | Mild | Moderate | Severe | |
| Clinical diphtheria | Complete, n(%) (n=16) | 1 (6.3) | 13 (81.3) | 2 (12.5) | 0.469[a] |
| | Incomplete, n(%) (n=16) | 1 (6.3) | 9 (56.3) | 6 (37.5) | |
| | No immunization, n(%) (n=39) | 2 (5.1) | 26 (66.7) | 11 (28.2) | |
| Confirmed diphtheria | Incomplete, n(%) (n=5) | 1 (20.0) | 3 (60.0) | 1 (20.0) | 0.610[b] |
| | No immunization, n(%) (n=12) | 0 (0.0) | 8 (66.7) | 4 (33.3) | |

[a]Spearman's correlation coefficient (rs) = 0.087; [b]rs = 0.133

**Table 4.** Analysis of immunization status and fatality

| Diphtheria status | Immunization status | Fatality status | | P value |
|---|---|---|---|---|
| | | Survived | Died | |
| Clinical diphtheria | Complete, n(%) (n=16) | 15 (93.8) | 1 (6.2) | 0.820 |
| | Incomplete, n(%) (n=16) | 14 (87.5) | 2 (12.5) | |
| | No immunization, n(%) (n=39) | 37 (94.9) | 2 (5.1) | |
| Confirmed diphtheria | Incomplete, n(%) (n=5) | 4 (80.0) | 1 (20.0) | 0.294 |
| | No immunization, n(%) (n=12) | 12 (100.0) | 0 | |

**Table 5.** Types of complications in diphtheria patients

| Complication, n | (n=26) |
|---|---|
| Bullneck only | 23 |
| Bullneck, shock, epistaxis | 1 |
| Shock, epistaxis | 1 |
| Shock, myocarditis | 1 |
| Total | 26 |

low percentage of positive culture results (17/71, 23.9%) was also noted by Puspitasari *et al.* in Dr. Soetomo General Hospital, Surabaya, Indonesia, in which only 22.8% of patients had positive culture results.[14] In addition, Rusmil *et al.* found that only 1.9% of subjects had positive cultures during the diphtheria outbreak in Cianjur District, West Java Province, Indonesia.[15] The relatively low percentage of positive culture results in

**Table 6.** Analysis of immunization status and complications

| Diphtheria status | Immunization status | Complications | | P value |
|---|---|---|---|---|
| | | No complications | With complications | |
| Clinical diphtheria | Complete, n(%) (n=16) | 14 (87.5) | 2 (12.5) | 0.013 |
| | Incomplete, n(%) (n=16) | 6 (37.5) | 10 (62.5) | |
| | No immunization, n(%) (n=39) | 25 (64.1) | 14 (35.9) | |
| Confirmed diphtheria | Incomplete, n(%) (n=5) | 2 (40.0) | 3 (60.0) | 0.620 |
| | No immunization, n(%) (n=12) | 7 (58.3) | 5 (41.7) | |

## Discussion

Of 71 subjects, 17 (23.9%) had positive culture results for *Corynebacterium diphtheriae*, with *mitis biovar* more common than *gravis biovar*. This finding was similar to those found in the studies of the 1990s outbreak in the newly independent states that formerly constituted the Soviet Union, in which mitis biovar predominated the culture results.[12,13] Two patients with gravis biovar were identified in our study. The first patient was identified in December 2011 and survived, but the second case was identified in July 2015 and died due to myocarditis. The diphtheria studies is due to the difficulty of growing Corynebacterium diphtheriae bacteria in the medium.[16] Limited laboratory facilities also contributed to the low percentage of subjects with positive culture results.[13] Since the Sampang District had inadequate facilities for culturing *Corynebacterium diphtheriae*, lab cultures were done at the Surabaya Laboratory of Health (*Balai Besar Laboratorium Kesehatan Surabaya*) in Surabaya, the capital of East Java Province.

In our study, both patient groups (clinical and confirmed diphtheria) had more female than male patients. Similarly, a Hyderabad, India study

had more female than male patients, ranging from pediatric to adult patients.[17] A multivariate analysis by Volkze et al. in Germany found that adult females had a weaker immune response in the form of lower antibody titers which also lasted for a shorter time than those in adult males. This weaker immune response made them 45% more susceptible to diphtheria than males.[18]

In our study, most patients were aged 5-9 years. This finding may be due to the waning of antibody titers from inadequate booster administration.[16] Diphtheria also occurred mostly in early childhood years (9 years and below) due to inadequate immune system performance.[16] School-aged children have increased frequency of contact with the disease-causing pathogen, leading to higher natural immunity to diphtheria.[19]

We found no correlation between immunization status and degree of diphtheria severity. A study during the outbreak in Buri Ram, Thailand also noted the absence of such a correlation.[20] Various studies showed that other factors, such as residential humidity, household density, and the wall type in houses had significant correlations with the severity of diphtheria.[21] Sampang District is endemic to diphtheria, so residents may have frequent contact with the disease-causing pathogen. Such a situation leads to higher natural immunity to diphtheria, enabling the diphtheria severity in patients to be compromised.[19] We did not measure patients' antibody levels, which might have shown a direct relationship between patient immunity and diphtheria severity.

We also found no correlation between immunization status and fatality of diphtheria patients. Previous studies have shown that low immunity due to poor nutrition, younger age, inadequate or absence of immunizations, and delayed treatment may increase the risk of death in diptheria patients.[22,23] However, immunization status was the sole variable, of those mentioned above (multifactorial), analyzed in this study. We also used the immunization status data from patient interviews, in addition to the Provincial Health Office data, which may have led to recall bias. Nevertheless, we consistently found that those with complete immunization status suffered less severe disease, and lower fatality, although the results were not statistically significant.

We found a statistically significant correlation between immunization status and complications in patients with clinical diphtheria, but not in those with confirmed diphtheria. The number of patients with confirmed diphtheria was significantly smaller than those with clinical diphtheria. Inadequate immunization may result in a higher risk of complications in diphtheria.[20] This is shown by a study of diphtheria among adult alcoholic patients in Sweden in which all patients with neurological complications had antibody titers below 0.01 IU/mL.[24] No similar study conducted on pediatric patients. Complete immunization was shown to increase the antibody titer in the recipients, possibly decreasing the probability of complications.[19] The absence of a correlation between immunization status and complications in patients with confirmed diphtheria was because none of the confirmed diphtheria cases had complete immunization status. Thus, in confirmed diphtheria cases, the risk of developing complications for incomplete and unimmunized patients was similarly higher compared to those with complete immunizations.

This study was limited as there were multiple sources of data: official medical records at the East Java Provincial Health Office, data obtained by the Diphtheria Research Team, and history-taking from diphtheria patients and their families. Data obtained from diphtheria patients and their families may have been subject to recall bias, causing inaccuracy of some parts of the data. In addition, we did not measure the antibody level against diphtheria toxin, so a more objective measurement could not be provided.

In conclusion, there is a significant correlation between immunization status and complications in patients with clinical diphtheria, but not in patients with confirmed diphtheria. This absence is likely because none of confirmed diphtheria cases have complete immunization for diphtheria.

## Conflict of Interest

None declared.

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