RISK FACTORS OF DIPHTHERIA CARRIERS IN INDONESIAN CHILDREN

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Abstract. Indonesia has one of the highest prevalence of diphtheria in the world, with East Java the most heavily affected. Despite the significant role of carriers in diphtheria transmission, studies in the country are still very limited. This study analyzed risk factors of children becoming diphtheria carriers using an observational case-control approach carried out from 2011 and 2015, which employed data from the East Java Provincial Health Office and the Main Health Laboratory [Balai Besar Laboratorium Kesehatan (BBLK)], Surabaya. Controls (4 controls for each carrier) were children who were in contact with diphtheria patients but did not have any microbiologically-confirmed *Corynebacterium diphtheriae* in nasal or throat swabs. The main variables were demographical and environmental risk factors. Analysis of 27 carriers and 108 controls, above two years of age, from Bangkalan, Jemberand Probolinggo districts identified the significant risk factor being paternal education (odds ratio = 5.5, 95% confidence interval: 1.6-19.4). There was no difference in immunization status, based solely on the memory of the caregivers, between the two groups. Thus, all efforts in the future should be prioritized on this risk factor.

Keywords: *Corynebacterium diphtheriae*, carrier, diphtheria, risk factor, Indonesian children

INTRODUCTION

Diphtheria outbreaks have occurred in Indonesia since 2004.The most heavily affected province was East Java, a region with 35 million population in Java Island, regarded as the most important island in the country (Ministry of Health, 2013; Hughes *et al*, 2015; Husada *et al*, 2017).

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Currently the prevalence of diphtheria in Indonesia is the second highest in the world after India (WHO, 2015). Research at the Newly Independent States (NIS) predicted several risk factors for the 1990-1996 diphtheria epidemics, namely, carriers, underlying disease of patients, personal hygiene, low coverage of immunization, economic crisis, militarization, massive mobilization of people, and changes of the pathogen biotypes (Vitek and Wharton, 1998; Quick *et al*, 2000; Meera and Rajarao, 2014; Nanthavong *et al*, 2015).

By identifying significant risk factors we will be able to prioritize future efforts to control outbreaks of diphtheria. One of the essential factors contributing to diphtheria outbreaks is the role of carriers (Vitek and Wharton, 1998; Meera and Rajarao, 2014), but there are limited studies on diphtheria carriers in Indonesia; a prevalence of diphtheria carrier in East Java was 1% in 2012 (Hughes *et al*, 2015). Hence, the objective of our study was to analyze the risk factors of becoming diphtheria carriers in children in East Java, Indonesia.

MATERIALS AND METHODS

Study area and population

This was an observational case-control study carried out on East Java Province, Indonesia. Cases were children in contact with diphtheria patients with (carriers) and without (healthy contacts or controls) microbiologically confirmed *Corynebacterium diphtheriae* in their nose or throat. All participants were 18 years of age or younger, and did not show any clinical signs or symptoms of diphtheria. Data were collected from East Java Provincial Health Office and the Main Health Laboratory [Balai Besar Laboratorium Kesehatan (BBLK)], Surabaya from January 2011 to August 2015. BBLK is a national reference laboratory for diphtheria in Indonesia. Both offices recorded all patients, carriers and healthy contacts who had culture data from nasal and throat swabs.

Ethical clearance for the study was granted by the Ethics Committee, Soetomo Hospital, Surabaya (Number 383/Panke.KKE/VII/2015). Prior informed consents were taken from all parents or legal guardians.

Laboratory procedures

Specimens from each swab (nose and throat) of the participants were placed in Amies transport media (Deltalab SL, Barcelona, Spain) and transported within 24 hours at 2-8^{o}C to BBLK, Surabaya where the specimens were cultured in Hoyle media (Oxoid, Basingstoke, Hampshire, UK) for 24-48 hours. Then, gram-positive colonies were re-cultured on Columbia agar (Oxoid, Basingstoke, Hampshire, UK) and subjected to a screening test using pyrazinamidase, cysteinase, urea, and nitrate (Efstratiou and Maple, 1994) and biochemical tests (API Coryne Test Kit; Biomerieux, Marcy l'Etoile, France). The final procedure step was a modified Elek test to check for toxigenicity (Engler *et al*, 1997). The whole process took 5-7 days.

Data analysis

Each registered carrier was matched with four controls based on age and district of residence. There were always "healthy contacts" for every diphtheria patient, but carriers were not always found. Thus carriers and controls might have come from different patients. Demographic data collected were age, sex, immunization status, personal hygiene, parental race or tribe, parental education and occupation, and house ventilation condition, the latter defined as the total area of the the windows in the house relative to total floor area. There were intervals of 6 months to 3.5 years between culture and demographic data collection. We also visited all participants, interviewed the parents or legal guardians, made physical examinations, and observed their houses. These field activities occured from March to July 2016. The time difference between culture results and field data collection varied from 6 months to 2.5 years. Data of risk factors were based on previous outbreak studies, particularly from Russia (Vitek and Wharton, 1998; Quick *et al*, 2000; Babirye *et al*, 2011; Besa *et al*, 2014; Meera and Rajarao, 2014; Wanlapakorn

et al, 2014; Nanthavong *et al*, 2015).

In addition to descriptive analyses, bivariate and multivariate analyses were performed using chi-square and logistic regression tests, with p-value < 0.05 and 95% confidence interval (CI) are considered statistically significant.

RESULTS

There were 35 carriers (≤18 years of age) identified during the study period, of whom 6 could not be located and 2 refused to participate, leaving only 27 carriers. Twenty-three (85%) carriers were recruited during 2012-2013. Carriers came from only nine districts (mainly Bangkalan, Jember and Probolinggo) compared to 21 districts with diphtheria patients. The two main identified diphtheria biotypes were mitis (n = 22) and gravis (n = 5). There were 108 controls from 14 districts. For the group aged 0-2 years old, there were no matched controls (n = 8) and the latter were recruited the nearest available age category.

Most samples were from children >2 years of age (Table 1). Although the immunization status was almost similar between carriers and controls, the latter group had a higher percent complete immunization status. The major parental race/tribe was Madurese. Many districts of interest were located in the northern part of the East Java Province. Significant differences between the carrier and control groups are paternal education and knowledge regarding diphtheria. The majority of participants lived in below-standard houses, despite a fair quality of clean water facilities (Table 2).

Among all risk factors described in Table 3, paternal education and knowledge about diphtheria are significant with odds ratio of 5.5 and 3.84, respectively. Using variables in a multivariate analysis, only one factor, paternal education, is significant (Table 4).

DISCUSSION

Diphtheria outbreak in East Java Province of Indonesia was declared in 2011 although increasing incidence has been observed since 2005 and up to 2016 more than 3,000 clinical diphtheria cases were reported (Husada *et al*, 2017), the most severe outbreak being in 2012 with almost 1,000 patients reported. Lack of microbiological facilities made culturing of nasal and throat swabs difficult to perform. All diphtheria biotypes were identified in the Province, but the the majority were mitis and gravis. The major affected areas were in the northern part of East Java including Madura Island. The inhabitants of this region are Madurese, one of the main race/tribe in the Province.

As one of the risk factors for diphtheria is the frequency of carriers, in particular children (Vitek and Wharton, 1998; Meera and Rajarao, 2014), our survey was conducted in children residing in East Java Province. The majority of carriers and controls were above 2 years of age, consistent with recent that the average age of incidence each year is shifting to the older age groups (Husada *et al*, 2014). During the outbreak in Russia in the 1990s most of the patients are adults (Vitek and Wharton, 1998; Galazka, 2000). In the Russian outbreak, many patients were women. In our study, although the proportion of girls among carriers were slightly higher, differences in age and gender are not statistically significant (Table 1). However, this phenomenon has not been fully understood (Kembabanova *et al*, 2000; Nekrassova *et al*, 2000; Meera and Rajarao, 2014).

Table 1
Demographic characteristics of children diphtheria carriers and controls residing in East Java Province, Indonesia during January 2011 to August 2015.

Characteristic	Participant		*p*-value
	Carrier (*n* = 27) *n* (%)	Control (*n* = 108) *n* (%)	
Age			
0-2 years	2 (7)	5 (5)	0.56[a]
>2-18 years	25 (93)	103 (95)	
Gender			
Male	11 (41)	57 (53)	0.438[a]
Female	16 (59)	51 (47)	
Immunization status			
Incomplete	13 (48)	41 (38)	0.334[a]
Complete before 1 year old	14 (52)	67 (62)	
Paternal ethnicity			
Madurese	12 (44)	49 (45)	0.796[a]
Others	15 (56)	59 (55)	
Maternal ethnicity			
Madurese	13 (48)	58 (54)	0.863[a]
Others	14 (52)	50 (46)	
Paternal education			
Elementary school	24 (89)	64 (59)	0.004[a]
Higher than elementary school	3 (11)	44 (41)	
Maternal education			
Elementary school	24 (89)	78 (72)	0.071[a]
Higher than elementary school	3 (11)	30 (28)	
Parent knowledge of diphtheria			
Poor	24 (89)	73 (68)	0.028[a]
Good	3 (11)	35 (32)	
Living in "pesantren"			
Yes	1 (4)	8 (7)	0.49[a]
No	26 (96)	100 (93)	
District			
Northern	25 (93)	96 (89)	0.572[a]
Others	2 (7)	12 (11)	

[a]Chi-square test."Pesantren", an Islamic traditional education center.

Diphtheria immunization coverage in the Madurese population generally is not high (Hughes *et al*, 2015), although there is no significant difference in that regard between carriers and controls in our study. Lacking diphtheria vaccination does not always means low immunity as people in the outbreak regions can get the immunity via natural infection (Hughes *et al*, 2015). The immunization coverage in Indonesia is worsening because of several external factors. The policy of giving a booster at the age of 18 months is somewhat new (Husada *et al*, 2014; Gunardi *et al*, 2018).

Table 2
Environmental characteristics of children diphtheria carriers and controls residing in East Java Province, Indonesia during January 2011 to August 2015.

Characteristic	Participant		*p*-value
	Carrier (n = 27) n (%)	Control (n = 108) n (%)	
Density of people residing in house			
≤2 people/8 m^2	8 (30)	42 (39)	0.373[b]
>2 people/8 m^2	19 (70)	66 (61)	
House ventilation[a]			
≥1/10 floor area	2 (7)	19 (18)	0.192[b]
<1/10 floor area	25 (93)	89 (82)	
Clean water source			
Good	9 (33)	54 (50)	0.121[b]
Poor	18 (67)	54 (50)	
Toilet and washing facilities			
Standard	22 (82)	91 (84)	0.727[b]
None	5 (18)	17 (16)	

[a]Total window area/total floor area. The requirement for total size of windows in every house in Indonesia is at least 5-10% of the total floor area (Ministry of Health of the Republic of Indonesia, 1999). [b]Chi-square test.

Previously, the first diphtheria booster for infant or toddler is given at the first grade of elementary school. Low coverage and long interval until the first booster tend to make children more susceptible to the infection (WHO, 2013).

We consider the accuracy of the interview-based data on immunization status should be supported by official records. However, because of limitations in human and time resources during the study, we could not verify the immunization documents. Previous studies argued that the memory of the caregivers might not be the proper source of data (Hughes *et al*, 2015; Nanthavong *et al*, 2015). This might explain why immunization status was not a significant risk factor. In addition, there is common knowledge by people in Indonesia that diphtheria vaccination is necessary only in the first year of life (Osaki *et al*, 2013; Gunardi *et al*, 2018). Many people do not have sufficient knowledge about diphtheria vaccine for children above 1 year of age.

We could not compare our data among people living in the central and southern parts of the Province to determine disparities of immunization coverage. Ethnicity and religion are significant contributors to the failure of immunization (Lakew *et al*, 2015). In East Java there have been many outbreaks of vaccine-preventable diseases, such as poliomyelitis (Estivariz *et al*, 2008). Social and cultural issues in relation to geographical and political aspects could play significant roles (Muryadi, 2006). Outbreaks in Lao PDR and Thailand were also influenced by such factors (Wanlapakorn *et al*, 2014; Nanthavong *et al*, 2015).

Paternal education was found to be an

Table 3
Bivariate analysis of risk factors of children diphtheria carriers residing in East Java Province, Indonesia during January 2011 to August 2015.

Variable	OR	95% CI	*p*-value
Gender	0.716	0.307-1.671	0.438
Male			
Female			
Age	0.607	0.111-3.312	0.560
>2-18 years			
<2 years			
Paternal ethnicity	1.118	0.48-2.602	0.334
Madurese			
Non-Madurese			
Maternal ethnicity	0.928	0.399-2.160	0.796
Madurese			
Non-Madurese			
Paternal education	5.50	1.560-19.392	0.004
Elementary school			
Higher than elementary school			
Maternal education	3.077	0.862-10.978	0.071
Elementary school			
Higher than elementary school			
Knowledge about diphtheria	3.836	1.081-13.604	0.028
Poor			
Good			
Immunization: Complete basic	1.517	0.649-3.547	0.334
Incomplete			
Complete			
District	1.563	0.328-7.438	0.572
Northern part			
Others			
Living in "pesantren"	0.481	0.058-4.018	0.490
Yes			
No			
Number of people living in house	1.511	0.607-3.763	0.373
>2 people			
<2 people			
Ventilation[a]	2.669	0.582-12.239	0.192
>1/10 floor area			
<1/10 floor area			
Clean water source	2.0	0.826-4.844	0.121
Poor			
Good			
Toilet and washing facilities	1.217	0.405-3.657	0.727
Standard			
None			

[a]Total window area/total floor area. The requirement for total size of windows in every house in Indonesia is at least 5-10% of the total floor area (Ministry of Health, Republic of Indonesia, 1999).

Table 4
Multivariate analysis of risk factors for children diphtheria carriers residing in East Java Province, Indonesia during January 2011 to August 2015.

Risk factor	β	aOR	95% CI	*p*-value
Paternal education: elementary school	1.705	5.5	1.560-19.392	0.008
Maternal education: elementary school	-0.082	0.921	0.169-5.009	0.924
Knowledge of diphtheria: bad	0.89	2.434	0.647-9.159	0.188
Clean water source: none	0.149	1.161	0.448-3.007	0.759

[a]OR, adjusted odds ratio; β, beta coefficients.

important contributing carrier risk factor. The role of fathers in the country's traditional society is very prominent. They decide all things in the family, including immunization acceptance, house location and its surroundings, and appropriate behavior of members of the family.Paternal education may have a connection with the risk of being a carrier, albeit indirectly. More studies are needed to clarify this issue.

Good education for parents will provide a broader understanding in decision making. The role of the mother concerning the decision-making process is not significant. Our finding is similar to a study in Uganda (Babirye *et al*, 2011). In other countries, the relationship between maternal knowledge and education was found to be more critical (Pokhrel and Sauerborn, 2004; Adhikari and Podishita, 2010). Inappropriate knowledge of diphtheria is also important; therefore public health efforts to improve knowledge and public understanding should always be pursued. In India and Malaysia, one of the causes of low immunization coverage is the limited knowledge (Angadi *et al*, 2013; Awadh *et al*, 2014). Educational regarding immunization hopefully can contribute much to improve the situation (Awadh *et al*, 2014).

Another traditional factor is living in "pesantren", an Islamic education center, which is widely spread all over the country. Like other traditional societies in many countries, they do not easily accept a more modern living style. Some refuse the immunization program. Their housing complex usually is below national standard requirements. Since thousands of people live in the same complex, the spread of infectious diseases could be very rapid. The government and many organizations have been trying to improve this condition (Sukana and Musadad, 2010; Ramdan *et al*, 2012). In the Russian outbreak, the military complex had the same situation (Vitek and Wharton, 1998).

Other contributing risk factors, such as the density of people living in the house, ventilation, sources of clean water, and toilet facilities were not significant between carriers and control groups. Many people were found to be living in poverty. These factors, together with personal hygiene, significantly affect *C.diphtheriae* transmission (Vitek and Wharton, 1998; Quick *et al*, 2000). Housing density also plays a role in the transmission of respiratory tract infections (Clark *et al*, 2002; WHO, 2007).

Based on the multivariate analysis only paternal education could be considered as a significant risk factor. This means that efforts in the future should be placed on improving the education of this target group. For many years mothers were the main target of interventions, but not the fathers (Rammohan *et al*, 2012; Herliana and Douiri, 2017; Jayanti *et al*, 2017; Holipah *et al*, 2018). This view needs to be changed. Future research focusing on the role of fathers and mothers in this Province should be pursued.

The limitation of this study was its retrospective design. Nevertheless, it would be difficult to conduct a prospective study considering the quality of microbiology laboratory performance. The other weakness was the accuracy of data on immunization status. The important roles of immunization coverage and immunity status have already been demonstrated in most parts of the world (Vitek and Wharton, 1998; Meera and Rajarao, 2014; Nanthavong *et al*, 2015). Every effort should be made to improve immunization coverage in this Province.

This study surveyed almost all diphtheria carriers in East Java. We also analyzed the role of *pesantren* and seasonal migrant workers. There have been insufficient studies on these two factors. The results of our study are expected to shape the direction of future efforts to solve the diphtheria outbreak problems in Indonesia.

In conclusion, this study highlights the role of paternal education as a significant risk factor for becoming diphtheria carrier among children in East Java, Indonesia. This aspect, together with knowledge about diphtheria infection, should be given priority in future intervention efforts.

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