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Risk factors for diphtheria in Sana'a, Yemen, 2019: a matched case–control study

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ABSTRACT

Objective: To identify risk factors for diphtheria related to sociodemographic, immunization and household status, and source of infection in Sana'a.

Methods: A retrospective matched case–control study (1:2 ratio) was conducted. Cases were defined as patients who met the World Health Organization's definition of confirmed diphtheria living in Sana'a between January and November 2019. Controls were defined as subjects without a history of diphtheria infection, living in the same neighbourhood, and matched with cases by age and sex. Crude odds ratios, adjusted odds ratio (aOR) and 95% confidence intervals (CI) were calculated to evaluate associations between risk factors and diphtheria.

Results: In total, 76 confirmed cases and 152 controls were enrolled in this study. Multi-variate analysis found significant associations between diphtheria infection and sharing a bedroom with at least two people (aOR 2.8, 95% CI 1.2–6.6), non-vaccination (aOR 2.6, 95% CI 1.2–6.0) and contact with a diphtheria case (aOR 10.6, 95% CI 2.6–43.6).

Conclusions: This study found that vaccination, not sharing a bedroom with at least two people, and isolation of diphtheria cases to prevent contact with non-infected individuals were the most important measures for protection of the community from diphtheria. Raising community awareness about vaccination, transmission and preventive measures is recommended.

Introduction

Diphtheria is a highly contagious and potentially life-threatening bacterial disease, caused by an exotoxin produced by *Corynebacterium diphtheria* (Allam et al., 2016). It causes airway obstruction due to nasopharyngeal infection. Diphtheria is transmitted from person to person by respiratory contact with a case (Dureab et al., 2019). The mortality rate of diphtheria is 5–10%, and is higher among young children (Rintani et al., 2018). Low immunization coverage, overcrowding, migration, parental education, nutritional status and source of transmission are factors that may influence the occurrence of diphtheria infection (Ramdan et al., 2018).

Globally, the number of reported cases of diphtheria has increased over recent years: 4535, 7102, 8819, 16,911 and 22,986 reported cases in 2015, 2016, 2018, 2018 and 2019, respectively (World Health Organization, 2020). Outbreaks have been reported in South Africa in 2015 and in sub-Saharan Africa since 2000 (Rintani et al., 2018) in a large

refugee camp for the Rohingya in Bangladesh in 2017; and in India, Indonesia and Nepal (Dureab et al., 2019).

In the Eastern Mediterranean Region, the number of reported cases of diphtheria increased as follows: 43, 25, 600, 3448 and 705 cases in 2015, 2016, 2017, 2018 and 2019, respectively (World Health Organization, 2020). Yemen had the highest number of reported cases from 2015 to 2019, followed by Pakistan (World Health Organization, 2020).

Diphtheria has become an important health problem in Yemen in recent years, although the last diphtheria outbreak prior to this was reported in 1980 (World Health Organization, 2020). On average, 50 cases of diphtheria have been reported annually since 2000 (Badell et al., 2021). However, as a result of the ongoing war since March 2015, only half of the health facilities in Yemen are partially or fully functioning, which has led to low immunization coverage and re-emergence of diphtheria outbreaks (Dureab et al., 2019). A diphtheria outbreak in October 2017 in Ibb spread to all governorates of Yemen (Badell et al., 2021),

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with nearly 556 probable cases and 52 deaths [9.4% case fatality rate (CFR)]. In addition, 2609 diphtheria cases including 128 deaths (5% CFR) were reported in 2018 [National Diphtheria Diseases Control Programme, Diphtheria Epidemiological Report, Ministry of Public Health and Population (MoPHP), 2019].

As a response to control the spread of diphtheria, MoPHP, in collaboration with the World Health Organization (WHO) and the United Nations Children's Fund, conducted three vaccination campaigns focused on high-risk areas in 2018 and 2019, targeting children between the ages of 6 weeks and 15 years (Expanded Program Immunization, Diphtheria Vaccination Campaigns Data, MoPHP, 2019). Despite efforts to control the diphtheria outbreak in 2018, almost 2033 probable cases including 131 deaths (6.4% CFR) were reported in 20 Yemeni governorates in 2019, and 1729 probable cases including 134 deaths (7.8% CFR) were reported in 2020 [Electronic Integrated Disease Early Warning System Program (eIDEWS), diphtheria data, MoPHP, 2021].

As a result of war and conflict in some governorates, residents left their homes and were displaced to other safe areas. Sana'a is one of the governorates that received many displaced families, resulting in overcrowding and a high rate of unemployment. Due to the reduced socio-economic status of these people, many families are living in poor housing conditions (e.g. many large families live in one room). This may play an important role in the increased risk of diphtheria infection.

Several studies have reported that low vaccination coverage, overcrowding and migration, and low income may represent important factors leading to the re-emergence of diphtheria in developing countries (Ramdan et al., 2018; Rintani et al., 2018). Other factors may also have influenced the incidence of diphtheria, such as level of education, shared utensils/cups, density, sharing a bedroom and family size, travel, and contact with diphtheria cases (Allam et al., 2016; Arifin and Prasasti et al., 2017; Ramdan et al., 2018; Quick et al., 2000; Suhendri and Ghazali et al., 2021).

To the authors' knowledge, no previous studies have investigated the risk factors for diphtheria in Yemen. As such, this study aimed to identify the risk factors for diphtheria related to sociodemographic, household and immunization status, and source of infection.

Methods

Study design, area and population

A matched case-control study (1:2 ratio) was conducted on confirmed cases of diphtheria in Sana'a, Yemen from October to December 2019. According to eIDEWS, Sana'a city is the governorate most affected by confirmed cases. Sana'a city has three diphtheria isolation units in Al Sabaen Hospital, Zaid Hospital and 22 May Hospital. A case-control study design was selected to determine the risk factors associated with diphtheria infection. Matching was performed to ensure that a similar proportion of subjects were in the same age group and of the same sex; for example, if 40% of the cases were males aged 2–29 years, 25% of the controls would be recruited with similar characteristics. This design improved the precision level.

Definitions

Cases

WHO's definition for a confirmed case of diphtheria was used. In this study, cases were defined as confirmed cases living in Sana'a city between January and November 2019.

Controls

Controls were defined as people living in the same neighbourhood of cases without a history of diphtheria since the start of the outbreak in 2017, and matched to cases by age and sex.

Sampling

All confirmed cases of diphtheria reported by eIDEWS from January to November 2019 were considered as cases. Two controls were selected for each case, and matched by age, sex and neighbourhood.

Controls were recruited from houses to the left of the case house. Only one control for each case from each house was selected. If there was no matched control in a house or the individual did not agree to participate in the study, controls were recruited from the next house.

Data collection and measurements

Data were collected using a pretested structured questionnaire through a face-to-face interview. The questionnaire was adapted from the literature (Ramdan et al., 2018; Quick et al., 2000) in the English language and translated into simple Arabic language. The questionnaire was validated by conducting a pilot study for nine participants who were excluded from this study. Any errors or unclear questions were revised. Trained female interviewers collected data by visiting the homes of cases. Participants aged ≥ 18 years and the parents of children aged < 18 years were interviewed.

Completed questionnaires were reviewed each day and checked for any incomplete or missing data. Ten percent of questionnaires were checked at random by supervisors through telephone calls or home visits.

The questionnaire consisted of closed-ended questions that covered sociodemographic characteristics (age; sex; district; education and occupation of cases, controls and parents). In addition, the questionnaire covered household data (type of house; family size and number of rooms in house; sharing of utensils, cups, towels and bedrooms), immunization status and source of infection (history of travel to areas with diphtheria, contact with diphtheria cases).

Data analysis and interpretation

EpiInfo Version 7.2 was used for data entry and analysis. Education level was categorized into low and high. Those individuals who were illiterate, those who could read and write, and those with a primary school education were classified as low education level, whereas individuals with a secondary school or university education were classified as high education level. Individuals who are working were compared with those individuals who are not working, including students. Preschool-age children were excluded from analyses of the association of diphtheria with educational and occupational status.

Continuous variables were categorized using mean or median based on data distribution. Frequency and percentage were used to summarize data. Univariate and multi-variate analysis by conditional logistic regression were used to calculate crude odds ratios (cOR) and adjusted odds ratios (aOR), respectively, and 95% confidence intervals (CI). $P < 0.05$ was considered to indicate statistical significance.

Results

In total, 76 confirmed cases of diphtheria and 152 matched controls were enrolled in this study. Of these, 60% were female, the median age of cases was 12.5 years [interquartile range (IQR) 6.0–28 years] and the median age of controls was 13 years (IQR 6.5–28 years). Thirty-four percent of participants were from Bani Al Harith district, and 44% had a low education level. Approximately 38% of participants were students, and 32% were not working (Table 1). The percentages of non-vaccinated cases and controls were 36% and 22%, respectively. Twenty percent of cases and 3% of controls had been in contact with diphtheria cases (Table 2).

Table 3 shows the non-adjusted and adjusted findings from the logistic regression analysis of factors associated with diphtheria. Univariate analysis found no significant differences between cases and controls for

Table 1
Distribution of sociodemographic characteristics of diphtheria cases and matched controls in Sana'a, 2019.

Characteristics	Cases (n=76)n (%)	Controls (n=152)n (%)	Total (n=228)n (%)
Age (years)			
Median age (interquartile range)	12.5 (6.0–28)	13 (6.5–28)	13 (6.0–28)
Sex			
Female	46 (60)	92 (60)	138 (60)
District			
Bani Al Harith	26 (34)	52 (34)	78 (34)
Al Sabaen	15 (20)	30 (20)	45 (20)
Ma'ain	11 (15)	22 (15)	33 (15)
Al Thawrah	8 (11)	16 (11)	24 (11)
Shu'aub	7 (9)	14 (9)	21 (9)
Al Whdah	5 (7)	10 (7)	15 (7)
Al Safiyah	1 (1)	2 (1)	3 (1)
Al Tahrir	1 (1)	2 (1)	3 (1)
Az'zal	1 (1)	2 (1)	3 (1)
Old Sana'a	1 (1)	2 (1)	3 (1)
Educational status			
Preschool-age children	20 (26)	33 (22)	53 (23)
Illiterate	7 (9)	14 (9)	21 (9)
Can read and write	1 (1)	2 (1)	3 (1)
Primary school	32 (42)	68 (45)	100 (44)
Secondary school	8 (11)	23 (15)	31 (14)
University	8 (11)	12 (8)	20 (9)
Occupational status			
Preschool-age children	20 (26)	33 (21)	52 (23)
Student	25 (33)	62 (41)	87 (38)
Working	10 (13)	7 (5)	17 (7)
Not working	21 (28)	50 (33)	72 (32)

Table 2
Household, immunization status and infection source characteristics of diphtheria cases and controls in Sana'a, 2019.

Characteristics	Cases (n=76)n (%)	Controls (n=152)n (%)	Total (n=228)n (%)
Household			
Type of house (apartment)	37 (49)	72 (47)	109 (48)
Family size of at least seven people (median)	40 (53)	92 (61)	132 (59)
Three or more rooms in house (mean)	43 (57)	90 (59)	133 (58)
Shared a bedroom with at least two people (mean)	63 (83)	108 (71)	171 (75)
Shared utensils and cups	69 (91)	136 (90)	205 (90)
Shared towels	34 (45)	60 (40)	94 (41)
Immunization status			
Non-vaccinated	27 (36)	33 (22)	60 (26)
Source of infection			
Travel history to area with diphtheria	8 (11)	14 (9)	22 (10)
Contact with diphtheria case	15 (20)	5 (3)	20 (9)

any sociodemographic factors. Among household risk factors, sharing a bedroom with at least two people was significantly associated with diphtheria (aOR 2.1, 95% CI 1.0–4.2). In addition, non-vaccinated status (aOR 2.3, 95% CI 1.2–4.6) and contact with a diphtheria case (aOR 9.1, 95% CI 2.6–31.5) were significantly associated with diphtheria infection (Table 3).

On multi-variate analysis, in comparison with controls, cases were more likely to share a bedroom with at least two people (aOR 2.8, 95% CI 1.2–6.6), and more likely to be unvaccinated (aOR 2.6, 95% CI 1.2–6.0). Moreover, cases were more likely to have been in contact with a diphtheria case (aOR 10.6, 95% CI 2.6–43.6) (Table 3).

Discussion

Diphtheria is a highly infectious and potentially life-threatening disease that can lead to increased morbidity and mortality rates, particularly among children. An outbreak of diphtheria occurred in Yemen in late 2017 and cases were still being reported in 2019. Studying the risk factors will provide valuable information that may help to improve understanding and control this outbreak.

This study found no association between sociodemographic factors and diphtheria infection. This result is similar to previous studies (Panduasa et al., 2012; Allam et al., 2016). In contrast, a systematic review in some developing countries, and studies conducted in Indonesia and Georgia showed that paternal education was a risk factor for diphtheria. This difference may be due to differences in the methodology and design of these studies (Husada et al., 2018; Rintani et al., 2018; Quick et al., 2000).

Regarding household factors, the present findings indicated that subjects who shared a bedroom with at least two people were three times more likely to have diphtheria. This result is in agreement with previous studies (Quick et al., 2000; Torikul Islam et al., 2020), but contrasts with a study by Panduasa et al. (2012), which may be due to the small sample size used in the latter study. Increasing community awareness about the need for isolation of cases with diphtheria infection will help to reduce the spread of disease among families.

Similar to the result of previous studies, the present study showed no association between diphtheria infection and type of house, family size, number of rooms, sharing utensils and cups, and sharing towels (Panduasa et al., 2012; Setiasih et al., 2012; Quick et al., 2000). How-

Table 3
Univariate and multi-variate logistic regression of risk factors associated with diphtheria in Sana'a, 2019.

Variables	Univariate		Multi-variate	
	cOR	95% CI	aOR	95% CI
Sociodemographic factors				
Paternal factors				
Low education level	0.8	0.4–1.4	0.6	0.3–1.5
Not working	1.3	0.6–2.8	1.1	0.5–2.5
Maternal factors				
Low education level	0.9	0.4–1.9	0.9	0.4–2.5
Not working	1.0	0.4–2.5	0.9	0.3–2.7
Household factors:				
Type of house (apartment)	1.1	0.6–1.9	0.9	0.4–1.8
Family size of at least seven people (median)	0.7	0.4–1.3	0.6	0.3–1.2
Three or more rooms in house (mean)	0.9	0.5–1.6	0.8	0.4–1.7
Shared a bedroom with at least two people (mean)	2.1	1.0–4.2 ^a	2.8	1.2–6.6 ^a
Shared utensils and cups	1.2	0.4–3.2	1.1	0.3–3.3
Shared towels	1.3	0.7–2.5	0.9	0.4–1.9
Immunization status				
Non-vaccinated	2.3	1.2–4.6 ^a	2.6	1.2–6.0 ^a
Source of infection				
Travel history to area with diphtheria	1.2	0.4–3.2	0.5	0.2–1.7
Contact with diphtheria case	9.1	2.6–31.5 ^a	10.6	2.6–43.6 ^a

aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio.

^a $P < 0.05$.

ever, a study in Bangladesh showed that daily sharing of food vessels was associated with diphtheria infection, whereas sharing towels was not associated with diphtheria infection (Torikul Islam et al., 2020).

Vaccination reduced the probability of diphtheria infection two-fold compared with non-vaccination. Increased access to routine immunization services and outreach visits should be strengthened for the prevention of diphtheria. The present finding of an association between immunization status and diphtheria infection is consistent with the findings of previous studies (Quick et al., 2000; Murakami et al., 2008, 2010; Panduasa et al., 2012; Setiasih et al., 2012; Bhattacharyya et al., 2016; Sein et al., 2016; Arifin and Prasasti et al., 2017; Rintani et al., 2018; Rahma and Purnomo et al., 2019; Wigrhadita, 2019; Suhendri and Ghazali et al., 2021). However, this was not found in a study in Indonesia (Husada et al., 2018). This difference may have been because the source of information for vaccination status was vaccination cards in the present study, compared with parent/caregiver recall in the Indonesian study.

This study found that travel history was not significantly associated with diphtheria infection, which was consistent with the results of previous studies (Panduasa et al., 2012; Setiasih et al., 2012).

Regarding contact with diphtheria cases, this study found an association with diphtheria infection. Individuals who had been in contact with a diphtheria case were 10-fold more likely to have diphtheria infection compared with those who had not been in contact with a diphtheria case. This supports the fact that diphtheria is very contagious, and is transmitted from person to person through direct contact with diphtheria cases. The present result was consistent with previous studies (Ramdan et al., 2018; Quick et al., 2000; Suhendri and Ghazali et al., 2021), but contrasted with the findings from Indonesia (Panduasa et al., 2012).

This study had a retrospective design, and may have been affected by recall bias, especially in terms of the immunization status of older participants. In addition, the small sample size may be considered as a limitation of the study. The results of this study may not be generalizable to all governorates in Yemen as it was performed in a single governorate.

In conclusion, many factors contribute to the occurrence of diphtheria infection in Sana'a. Contact with a diphtheria case was the main risk factor associated with infection. Moreover, sharing a bedroom with at least two people and non-vaccination facilitate transmission of diphtheria among healthy people.

Preventive efforts should focus on increasing immunization coverage among the population by strengthening routine immunization, and increasing community awareness of the need for isolation of cases during the infectious period. Further case-control studies should include more governorates including urban and rural areas.

Declaration of Competing Interest

None declared.

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Availability of data and materials

All relevant data are presented in this paper, and more information can be provided upon reasonable request from the corresponding author.

Ethical approval and consent to participate

This study was approved by the Research and Ethics Committee at MoPHP in the Republic of Yemen. An official letter for permission to conduct the study was sent from MoPHP to Sana'a City Health Office. The study was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants, and parents of children aged <18 years. Confidentiality of data was assured and ensured.

Author contributions

AAHN was the principal author involved in the concept, design and implementation of the study; analysis and interpretation of data; and manuscript preparation. MAA was involved in the analysis, and the final report and manuscript revision. YG was involved in the final manuscript revision. All authors reviewed and approved the final version of the manuscript.

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