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Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic

E. E. JONES,[1] R. J. KIM-FARLEY,[2] M. ALGUNAID,[3] M. A. PARVEZ,[4] Y. A. BALLAD,[3] A. W. HIGHTOWER,[1] W. A. ORENSTEIN,[2] & C. V. BROOME[1]

Between 29 August 1981 and 16 January 1982, an epidemic of diphtheria produced 149 cases in Hodeida, Yemen Arab Republic. The overall attack rate was 11.8 per 10 000; the most frequent victims were males under 5 years of age, with an attack rate of 55.7 per 10 000. Severity of the illness varied inversely with age and the number of previous doses of DPT. A case-control study showed that vaccination with DPT was protective (P = 0.03) with an efficacy of 87.3% (95% confidence interval, 32.2–99.5%) among those who had received 3 or more doses. Risk factors for the development of disease were previous contact with a case (P = 0.002), previous contact with a person having skin disease (P = 0.04), obtaining drinking-water from a wheeled carrier (P = 0.008), and consumption of factory-made yoghurt (P = 0.003). The secondary attack rate among household contacts under 15 years of age was at least 1.3%.

Diphtheria is rarely seen in developed countries owing to the availability of an effective vaccine. Outbreaks have occurred, however, among inadequately vaccinated segments of the population, and several modes of transmission have been suggested (*1-6*). Although large segments of the population in many developing countries are unvaccinated, outbreaks of diphtheria are documented rarely (*7*). During the period August 1981 through January 1982, an outbreak of diphtheria occurred in Hodeida, Yemen Arab Republic, which offered an opportunity to evaluate the mode of spread of diphtheria among a largely unvaccinated population in a developing country.

BACKGROUND

Hodeida, Yemen's major Red Sea port, has a population of approximately 126 000. The 509-bed Al-Olafi Hospital, built in 1974 and located in Hodeida, serves as the only referral hospital of the Tihama, Yemen's coastal plain. The hospital maintains a medical records department where all charts are filed and rosters of admission and discharge diagnoses are maintained. Monthly statistics are compiled using the World Health Organization (WHO) list of reportable diseases (*16*). Diphtheria has been included on this list since November 1979.

A vaccination programme was begun in Hodeida in 1977 by the Expanded Programme on Immunization (EPI), supported by WHO. As part of this programme, children under the age of 5 years were immunized with DPT, BCG, and oral polio vaccines. According to EPI estimates, approximately 40% of children less than 5 years of age residing in Hodeida had received at least 1 DPT vaccination prior to August 1981; 13% had received a complete series of 3 vaccinations.

METHODS

Hospital-based study

Case definition: a clinical case of diphtheria was defined as illness in an individual examined by a hospital physician and diagnosed as diphtheria. A laboratory-confirmed case was defined as a patient with clinical illness from whom a culture processed at Al-Olafi Hospital yielded *Corynebacterium diphtheriae*.

[1] Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA 30333, USA. Requests for reprints should be sent to Dr Ellen E. Jones at this address.

[2] Immunization Division, Center for Prevention Services, Centers for Disease Control, Atlanta, GA, USA.

[3] Tihama Area Ministry of Health, Hodeida, Yemen Arab Republic.

[4] WHO Epidemiologist, San'a, Yemen Arab Republic.

Co-primary case: a second case occurring in a household within 1 day of the first case.

Secondary case: a case with onset 7 or more days after onset of the first case in a household.

Possible secondary case: a case which occurred either 2–6 days or an undetermined number of days after the onset of the first case.

The hospital records of all cases were reviewed for the following information: date of onset of illness, date of hospitalization, home address, age, sex, vaccination status, indicators of clinical severity, anatomical involvement, therapy with antimicrobials and antitoxin, tracheostomy, length of hospital stay, illness among siblings, and outcome.

Hospital records since January 1975 were also reviewed to determine whether any additional cases of diphtheria had occurred prior to the epidemic.

Clinical severity and anatomical involvement were defined as follows:

Clinical severity: (1) mild—localized symptoms, i.e., sore throat; (2) moderate—systemic effects, i.e., respiratory distress or temperature $\geqslant 39$ °C; (3) severe—tracheostomy recommended or death.

Anatomical involvement: symptoms and/or signs involving the nares, pharynx, larynx, skin, and conjunctiva, singly or in combination.

Vaccination status was ascertained from hospital records, informant recall, individual vaccination records, or paediatrician's statement.

Laboratory investigations

Pharyngeal swabs obtained from patients prior to or during hospitalization were cultured using Loeffler's or tellurite media (*8*, *9*). Positive cultures from patients admitted to the Al-Olafi Hospital during the outbreak were subcultured on to Pai media for transport to the Centers of Disease Control (CDC), Atlanta, Georgia, where the organisms were typed and tested for toxin production (*10-12*).

We compared the effectiveness of Pai and silica gel transport media using pharyngeal swabs obtained from patients on admission to the hospital. To estimate carriage rates of *C. diphtheriae* in the community, we took pharyngeal and nasopharyngeal cultures from every third child who visited the outpatient clinic for DPT vaccination on 12 January 1982.

Case-control survey

Addresses were available for only 47 of the 149 infected children, representing 32 households. The 47 cases and 94 controls (matched for age, sex, and geographical location) were surveyed for previous contact with cases of diphtheria, exposure to cutaneous disease in others, vaccination status of all children under 15 years of age in the household, hygienic habits, exposure to dairy products, water sources, indicators of crowding, animal contact, and socioeconomic status.

Statistical methods

The statistical significance of the differences between proportions was evaluated by Fisher's exact test, two-tailed. In the case-control study, variables were analysed using a matched linear logistic regression model (*13*). Two multivariate models were developed: (1) a model in which all cases for whom addresses were available and their controls were represented, (2) a model in which only the index and co-primary cases were included. Using the rare disease assumption, the odds ratio approximates the relative risk.

Vaccine efficacy was calculated using the relative risk estimate from the multivariate model including all cases, and was therefore adjusted for the presence of other significant risk factors. Never immunized children, 0–9 years of age, were compared with those fully immunized (3 or more doses of DPT).

RESULTS

Hospital-based study

From January 1975 to December 1979, only 1 case of diphtheria was reported at the Al-Olafi Hospital. Eleven cases occurred in 1980 and 3 cases occurred in 1981 prior to the outbreak, 2 in March and 1 in April.

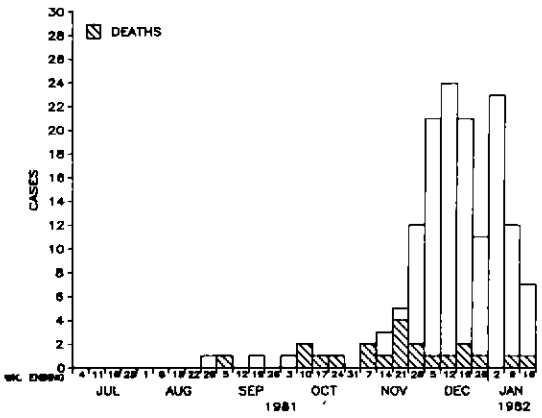

Fig. 1. Number of cases of diphtheria, by week of admission, in Hodeida, Yemen Arab Republic, 29 August 1981 to 16 January 1982.

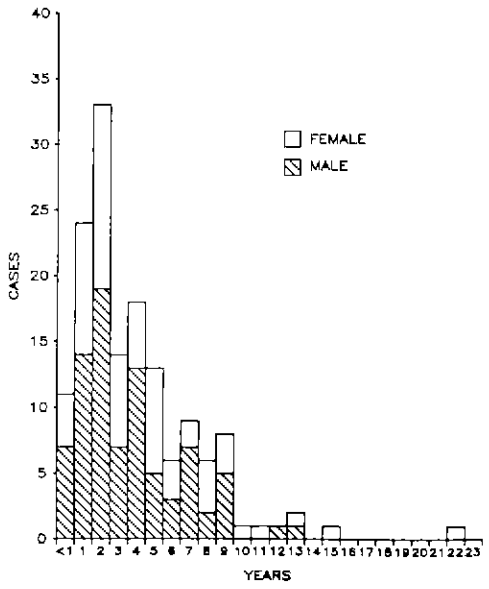

Fig. 2. Number of cases of diphtheria, by age and sex, in Hodeida, Yemen Arab Republic, 29 August 1981 to 16 January 1982.

Between 29 August 1981 and 16 January 1982, 149 patients with diphtheria were admitted to the hospital (Fig. 1). Fifty-seven cases were laboratory confirmed (54% of the 106 cases cultured); 21 resulted in death, a case-fatality rate (CFR) of 14%.

Children less than 5 years of age accounted for 68% of the cases (Fig. 2) and had the highest attack rate (46.5 per 10 000 population). The attack rate tended to be higher for males than for females in this age group (55.7 and 37.3 per 10 000 population, respectively; $P = 0.06$). Although the CFR for males was higher than for females (16.7% and 9.3%, respectively), males could not be shown to have significantly more severe disease than females. Males and females were similar in culture positivity, presence of a membrane, and vaccination status. In those over 5 years of age, the attack rates for males and females were similar.

Children under 5 years of age had the most severe disease (Table 1). In this age group 24% (23 of 98) had severe disease, as opposed to only 5% (2 of 40) of those aged 5–9 years ($P < 0.001$). All but 2 of the 21 children who died were less than 5 years of age. Clinical severity by vaccination status is shown in Table 2. In the group less than 5 years of age, vaccinated children had less severe disease than did unvaccinated children ($P = 0.0007$). However, age was an independent factor for disease severity, because unvaccinated children less than 5 years old had more severe illness than unvaccinated children 5–9 years old ($P = 0.005$). Although the absolute number of cases of moderate and severe disease remained relatively constant as the epidemic continued, an increasing number of less severe cases of diphtheria were seen at the hospital. This can in part be explained by a change in admission policy: culture-positive patients were admitted regardless of clinical presentation. During the period 29 August to 18 December 1981, 50 out of 90 children admitted were cultured for *C. diphtheriae*. Cultures were positive in 30% (15 of 50) of these children. From 19 December to 16 January 1982, 59 children were admitted: 56 of these were cultured, and in 75% (42 of 56) the cultures were positive.

The anatomical locations involved with diphtheria were as follows: pharyngeal only, 80.5%; laryngeal and pharyngeal combined, 14.1%; pharyngeal and either nasal or ocular, 2.0%; laryngeal only, 1.3%; not recorded, 2%. No lesions consistent with cutaneous diphtheria were noted.

Of 80 patients having pharyngeal and/or laryngeal disease, 31% had evidence of a membrane.

Table 1. Clinical severity of diphtheria cases by age[a]

Age (years)	Number of cases			
	Mild	Moderate	Severe	Total
0–4	58 (59)[b]	17 (17)	23 (24)	98
5–9	38 (95)	0	2 (5)	40
10–14	4 (100)	0	0	4
⩾ 15	2 (100)	0	0	2
Total	102	17	25	144

[a] Excludes 5 children for whom clinical severity is unknown

[b] Figures in parentheses are percentages

Table 2. Clinical severity by age and by diphtheria toxoid vaccination status[a]

Age group and number of vaccinations	Number of cases			
	Mild	Moderate	Severe	Total
0–4 years				
0	29 (51)[b]	12 (21)	16 (28)	57
1	13 (93)	1 (7)	0	14
2	0	0	0	0
⩾ 3	5 (100)	0	0	5
Total	47	13	16	76
5–9 years				
0	16 (89)	0	2 (11)	18
1	9 (100)	0	0	9
2	1 (100)	0	0	1
⩾ 3	5 (100)	0	0	5
Total	31	0	2	33

[a] Excludes 34 children (0–9-years old) for whom vaccination status or clinical severity could not be determined.
[b] Figures in parentheses are percentages

Table 3. Results of matched univariate analysis of all cases and controls (46 sets)

Characteristics	Cases (%)	Controls (%)	Relative risk	Confidence interval
Vaccination status				
1–2 vaccinations	60	74	0.60	0 27–1.32
⩾ 3 vaccinations	11	33	0 25	0 08–0 78
Contact with a case	43	6	31.65	4 22–237 5
Contact with skin disease	22	7	3.84	1 16–12.7
Obtained drinking-water from wheeled carrier	26	10	10.28	1 24–85.21
Milk and milk products:				
Raw milk	17	7	4.25	0 83–21 9
Factory-made yoghurt	60	24	3 88	1.71–8.8
Cheese	85	71	2.08	0 69–6 25
Ice-cream	51	36	2 15	0.97–4.74

Laboratory results

Of the 106 patients from whom cultures were made at Al-Olafi Hospital, 57 (54%) cases of diphtheria were confirmed in the hospital laboratory by isolation of *C. diphtheriae* (Table 3). Twenty-two of 66 isolates from patients (33%) (representing 18 out of 46 patients) were available and were confirmed in the CDC laboratory.

Nineteen cases had swabs directly plated on Pai and silica gel transport media. Ten swabs yielded positive cultures following holding and transport of at least 6 weeks duration: 3 from Pai alone, 3 from silica gel alone, and 2 from both. Swabs were also obtained

from 16 of these 19 children for culture at the Al-Olafi Hospital: 44% (7 of 16) were positive. Four of these 7 positive at Al-Olafi were positive when tested in CDC. An additional 4 swabs from patients who were negative at Al-Olafi Hospital, were positive when cultured at CDC.

C. mitis isolated from 25 patients (33 isolates) for whom positive cultures were obtained after transport to CDC of either pharyngeal swabs or swabs from positive cultures in the Al-Olafi Hospital. Organisms isolated from 22 patients were toxin producers; 22% (5 out of 22) of these patients had either moderate or severe disease. All 3 of the non-toxin-producing strains of *C. mitis* were associated with mild illness.

None of the pharyngeal and nasopharyngeal swabs taken from 93 children who came to the clinic for DPT vaccination and cultured at CDC were positive for *C. diphtheriae*.

Case-control study

All 47 patients included in the case-control study were admitted to the hospital between 5 December and 9 January. All had mild disease, and 66% were laboratory confirmed; there were 20 males and 27 females. Six households had multiple cases, accounting for 16 of the 47 cases. In three households, onset of illness of subsequent cases was within 1 day of the initial case, representing co-primary illness (6 cases). In one household, 2 secondary cases occurred 7 days after onset of the initial case (3 cases). In two households, the date of onset of cases was unclear, and the distinction between co-primary and secondary cases could not be made (8 cases). Results of univariate analysis are summarized in Table 3.

Multivariate logistic regression analysis of information on all cases and controls revealed that previous contact with a case of diphtheria ($P = 0.002$, relative risk (RR) = 71.04) and previous contacts with a person having skin disease ($P = 0.04$, RR = 41.91) were risk factors for the development of diphtheria. One, two or three vaccinations with DPT were protective ($P = 0.03$, RR = 0.13). Vaccine efficacy was 87.3% (95% confidence interval, 32.2–99.5%). Obtaining drinking-water from a wheeled carrier[a] ($P = 0.008$, RR = 28.42) and ingestion of factory-made yoghurt ($P = 0.003$, RR = 14.92) were also significantly and independently associated with illness. Neither ingestion of home-made yoghurt nor drinking raw milk was associated with illness on univariate ($P > 0.10$, RR = 0.67; and $P > 0.05$, RR = 4.25, respectively) or multivariate analysis.

Multivariate analysis of information obtained from index and co-primary cases revealed the following. Previous contact with a case and previous contact with a person having skin disease were no longer significant. Full vaccination (3 ore more does of DPT) was protective ($P = 0.04$, RR = 0.14); 1, 2 or 3 vaccinations tended to be protective (RR = 0.50 on univariate analysis, efficacy = 50%), although this trend was not significant The association of disease with factory-made yoghurt ingestion and contact with a wheeled drinking-water carrier remained significant ($P = 0.005$, RR = 9.91; and $P = 0.04$, RR = 10.84, respectively). Although these factors could not be evaluated further by logistic regression in the subpopulation of cases that were laboratory confirmed and/or in which membrane was present, they were significant in this subpopulation by univariate analysis.

The secondary attack rate based on definite cases of secondary disease was 0.9% within households, a 7.6-fold increase over the risk in the general population, and 2.6% in contacts less than 15 years of age, a 22-fold increase in risk in this age group.

DISCUSSION

In this outbreak of diphtheria, two types of cases occurred: (1) primary cases, and (2) cases occurring among those with a history of household contact with an earlier case. Transmission of infection from case to case, especially within a household, has been well described. The vehicle for transmission of infection to primary cases is harder to determine. In addition to risk factors for diphtheria described previously, our data suggest a role for foodborne transmission of diphtheria among primary cases.

While no one factor accounts for the epidemic, several risk factors, identified by the case-control study, probably contributed to its development. First, vaccination levels within the community were low. Despite efforts at improving vaccination coverage during the preceding 3 years, only an estimated 13% of children less than 5 years of age and 1% of those aged 5–9 years had been fully vaccinated at the onset of the epidemic The cases were therefore significantly less likely to have been vaccinated than the controls.

Second, cases had significantly more previous contact with persons having skin disease than did controls. Although the type of skin lesion could not be characterized, other studies have shown high rates of respiratory colonization among contacts of patients with cutaneous diphtheria, suggesting that exposure to cutaneous disease may be important in the acquisition of respiratory infection (3).

Third, an association was found with obtaining water from a wheeled carrier rather than from wells or faucets. Diphtheria is not thought to be a water-borne

[a] One of a fleet of trucks which carries water obtained from wells outside the city to neighbourhoods within Hodeida

illness, so it is possible that contact with the driver of a wheeled carrier may have been contributory. Two families who obtained water from this source used the same driver and stated that they had noted extensive skin lesions on his arms.

Several outbreaks of diphtheria have been described in Britain and the United States in which a milk-supply has been implicated as the vehicle of infection (*6, 14, 15*). The organism has been isolated from the nasopharynx of persons handling the milk or in ulcers found in the teats of cows. The organism has also been isolated from milk.

Although we were unable to implicate ingestion of raw milk in this outbreak of diphtheria, the possible importance of yoghurt ingestion in the development and spread of illness is intriguing and has not been mentioned before in the literature. The occurrence of epidemic disease, the distribution of the outbreak in many neighbourhoods of the city, and the results of the case-control study are consistent with an outbreak due to an item of contaminated food that has city-wide distribution, i.e., yoghurt. While it is also possible that factory-made yoghurt might have been ingested as a result of pharyngeal discomfort associated with early diphtheria, this is unlikely because cases were less likely than controls to consume home-made yoghurt. Further delineation of the role of factory-made yoghurt should be investigated during future outbreaks.

Several control measures were tried out. Erythromycin chemoprophylaxis was recommended for household contacts of cases, and a mass vaccination campaign was begun. In addition, continued surveillance was attempted by requiring maintenance of an ongoing record in the paediatric ward of the name, age, sex, address, and vaccination status of all children who were diagnosed with diphtheria. This record was to be checked regularly by representatives of the Ministry of Health in order to provide erythromycin to household contacts of newly diagnosed cases and to direct the vaccination programme to areas with the highest attack rates.

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RÉSUMÉ

DIPHTÉRIE: FLAMBÉE POSSIBLE PAR CONTAMINATION ALIMENTAIRE A HODEIDA, À LA RÉPUBLIQUE ARABE DU YÉMEN

Entre le 29 août 1981 et le 16 janvier 1982, la ville d'Hodeida (République arabe du Yémen) a connu une épidémie de diphtérie totalisant 149 cas, épidémie qui a permis d'évaluer le mode de propagation dans une population pour la plupart non vaccinée dans un pays en développement. Le taux global d'atteinte était de 11,8 pour 10 000; les plus touchés étaient les garçons de moins de cinq ans (taux d'atteinte: 55,7 pour 10 000). La gravité de la maladie était inversement proportionnelle à l'âge et au nombre de doses antérieures de DTC.

On a isolé *Corynebacterium mitis* à partir de 25 malades pour lesquels on disposait de cultures positives après transport aux Centers for Disease Control d'Atlanta, en Georgie (Etats-Unis), soit de prélèvements pharyngés ou de prélèvements tirés de cultures positives de l'hôpital Al-Olafi d'Hodeida. Les organismes prélevés sur 22 des malades étaient toxinogènes.

On connaissait l'adresse de 47 des 149 enfants infectés. On a étudié ces 47 cas et 94 cas témoins, d'âge, de sexe et de lieu de résidence correspondants. Il ressort de l'étude que la vaccination au DTC était protectrice ($P = 0,03$), avec une efficacité de 87,3% (intervalle de confiance à 95%, 32,2–99,5%), chez les sujets qui avaient reçu trois doses ou davantage. Les facteurs de risque présentant une certaine importance pour l'affaition de la maladie étaient le contact avec une personne atteinte ($P = 0,002$), le contact avec une personne affectée d'une maladie de peau ($P = 0,04$), la consommation d'eau livrée par camion ($P = 0,008$), et la consommation de yoghourt industriel ($P = 0,003$).

Dans cette épidémie, on a relevé deux types de cas: 1) les cas primaires, 2) les personnes vivant dans un foyer où un cas s'était déclaré antérieurement. La transmission de l'infection dans les familles est bien documentée, mais la source d'infection dans les cas primaires est plus difficile à

cerner. Outre les facteurs de risque de diphtérie évoqués précédemment, les données en notre possession donnent à penser que dans les cas primaires l'infection serait transmise par les aliments.

Nous n'avons pas pu incriminer l'ingestion de lait cru dans la présente flambée de diphtérie, mais l'importance éventuelle de la consommation de yoghourt dans le développement et la propagation de la maladie n'est pas sans intérêt et elle n'a jamais été mentionnée auparavant dans les ouvrages spécialisés. Le caractère épidémique, la distribution des cas dans de nombreux quartiers de la ville, les résultats de l'étude cas-témoins accréditent l'idée d'une flambée due à un aliment contaminé distribué dans toute la ville, par exemple le yoghourt. Certes, il est possible que les patients aient tout simplement mangé du yoghourt industriel parce qu'ils avaient mal à la gorge durant la première phase de la maladie, mais ce n'est guère probable car les malades avaient moins de chances que les cas témoins de consommer du yoghourt fait à la maison. Il y aurait lieu d'étudier plus avant, lors d'épidémies futures, le rôle des aliments comme véhicule de *C. mitis*

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