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Risk factors for typhoid fever among adult patients in Diyarbakir, Turkey

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SUMMARY

We conducted a case-control study to assess risk factors for typhoid fever in Diyarbakir, Turkey, a region where transmission of *Salmonella typhi* is endemic. We prospectively identified febrile patients from Diyarbakir and the surrounding area who were admitted to hospital. Cases were defined as patients who had *S. typhi* isolated from at least one blood culture. Sixty-four cases with blood culture-confirmed *S. typhi* were identified between May 2001 and May 2003. In total, 128 age- and sex-matched controls selected from neighbourhoods as cases were enrolled. We hypothesized that consumption of raw vegetables contaminated with sewage would be associated with an increased risk of typhoid fever. Conditional logistic regression modelling revealed that living in a crowded household (OR 3·31, 95% CI 1·58–6·92, $P=0·002$), eating *cig kofte* (a traditional raw food) (OR 5·29, 95% CI 2·20–12·69, $P=0·000$) and lettuce salad (OR 3·55, 95% CI 1·52–8·28, $P=0·003$) in the 15 days prior to symptoms onset was independently associated with typhoid fever. We conclude that living in a crowded household and consumption of raw vegetables outside the home increase the risk of typhoid fever in this region.

INTRODUCTION

Typhoid fever, caused by the bacterium *Salmonella typhi*, is an important global health problem. It is estimated that 16 million cases occur annually worldwide [1, 2]. Endemic in countries where there is neither a safe water supply nor adequate sanitation [3, 4], *S. typhi* is spread through faecal contamination of water and food [5–7]. Typhoid fever is a particularly serious public health problem in southeast Turkey, where 10 000 patients are diagnosed annually with this condition [8].

Despite the large public health burden, few reports exist about risk factors for transmission of typhoid fever in endemic areas [6, 9–12]. Most epidemiological investigations of *S. typhi* transmission were conducted during acute typhoid fever outbreaks [13]. Among other factors, these studies have identified food handlers as an important source of transmission in outbreaks [14, 15]. However, given the limited generalizability of data derived from outbreaks, it is important to understand the risks for endemic transmission.

At Dicle University Hospital in southeast Turkey, 5% of all positive blood cultures are of *S. typhi* [16].

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To develop a rational control strategy, the identification of risk factors and relevant route of *S. typhi* transmission is essential. High rectal carriage rates of *S. typhi* among workers at a plantation located near Diyarbakir have previously been demonstrated [17]. Sewage water is used to irrigate soil from which vegetables are distributed to a population residing within a 150-km radius of the plantation. Understanding the risk factors for typhoid fever in this region could help with preventative measures.

To identify risk factors for developing typhoid fever in Diyarbakir city and its surroundings, we conducted a case-control study. We hypothesized that consumption of raw vegetables would be associated with risk of typhoid fever.

MATERIAL AND METHODS

Setting

Diyarbakir, with a population of about 1·3 million, is the largest city in southeast Turkey. Dicle University Hospital is a 1050-bed hospital offering primary, secondary, and tertiary care to surrounding towns and cities.

Design

Between May 2001 and May 2003 we prospectively identified patients who were admitted to Dicle University Hospital with fever, defined as a temperature of $\geqslant 38\,^{\circ}C$. Patients who were not from Diyarbakir and the surrounding area were excluded, as were patients who had travelled outside of Diyarbakir in the 4 weeks prior to symptom onset. The study was limited to persons aged $\geqslant 15$ years. At least two blood culture specimens were collected from each patient. Five to 10 ml of blood was collected into blood culture vials (aerobic) containing antibiotic-absorbing resins (Becton Dickinson Diagnostic Inc., Sparks, MD, USA).

Case-patients were defined as patients who had *S. typhi* isolated from at least one blood culture.

Controls were selected from the same neighbourhood as cases. Two controls, with no current fever or history of typhoid fever, were matched by sex and age (within 2 years) to case-patients. Potential controls who reported 2 days of consecutive fever within the preceding 4 weeks or who had travelled outside of Diyarbakir in the preceding 4 weeks were ineligible. Neighbourhood controls were selected in a standardized manner. Potential controls who lived in a home on the right-hand side of the case-patient's house were approached, and if no suitable control was found, the house on the left-hand side of the case-patient's home was approached. If still unsuccessful, this was followed by approaching occupants of the second house on the right, followed by the second house on the left if unsuccessful. This process was repeated until households five houses away from the case household were approached.

We collected demographic information (age, sex) from each case-patient and control using a standardized questionnaire. Case-patients were interviewed in the hospital or at their home by a member of the research team and were asked about food and drink items consumed, eating outside the home, household factors, and handwashing practices in the 2 weeks prior to onset of symptoms. These questions were based in part on locally available foods, food items we hypothesized as likely vehicles for *S. typhi* transmission and foods identified in previous published investigations of *S. typhi* outbreaks. Controls were interviewed in their homes with respect to practices and consumption patterns in the 2 weeks prior to the interview.

Laboratory studies

Positive blood culture vials were subcultured to blood agar and EMB agar plates (Oxoid, Basingstoke, Hampshire, UK). Non-lactose-fermenting colonies on EMB agar were biochemically identified as *S. typhi* by using Vitek identification system (bioMerieux, Vitek Inc., Hazelwood, MO, USA). Serological identification of *S. typhi* was not included into the study because of low sensitivity and specificity of the tests.

Statistical analysis

All data entry and analysis was performed using SPSS 9.05 for Windows (SPSS Inc., Chicago, IL, USA). A χ^2 test was used for binary variables and Student's t test for continuous variables. A matched odds ratio (OR) with exact confidence limits was calculated for categorical exposures. We conducted conditional logistic regression where candidate variables with a P value $<0{\cdot}1$ were entered using a backwards, logistic regression analysis approach. Variables with $P>0{\cdot}05$ were removed from the model.

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Table 1. *Univariate analysis of risk factors for typhoid fever among 64 cases and 128 age- and neighbourhood-matched controls, Diyarbakir, Turkey*

Risk factor	Cases (%)	Controls (%)	OR	95% CI	*P* value
No toilet in household	4	5	0·61	0·16–2·35	0·469
Soap in toilet	49	97	1·04	0·52–2·11	0·905
Tap water in toilet	53	113	0·64	0·76–1·49	0·296
Living in a crowded household*	30	32	2·65	1·41–4·99	0·002
Municipality drinking water	55	114	0·75	0·31–1·84	0·530
Consumption of beverages or water outside home	29	37	2·04	1·09–3·8	0·024
Eating outside home	28	29	2·66	1·39–5·06	0·003
Eating *food containing* raw leafy vegetables					
Lettuce with *cig kofte*	30	11	9·39	4·26–20·67	0·000
Lettuce alone	31	14	7·65	3·65–16·04	0·000
Green salad	18	7	6·76	2·65–17·26	0·000
Vegetables with kebab	14	10	3·30	1·37–7·94	0·007
Eating suspected food	1	7	0·27	0·03–2·28	0·202
Eating food from street vendors	14	19	1·61	0·75–3·46	0·223
Washing hands before eating	57	109	1·42	0·56–3·58	0·456
Antimicrobials in the 2 weeks prior to symptom onset	1	8	0·238	0·029–1·946	0·147

OR, Odds ratio; CI, confidence interval.

* Defined as more than the mean value of household members per room for all participants (>2·25).

RESULTS

Sixty-four case-patients and 128 age- and sex-matched neighbourhood controls were enrolled. Case-patients and controls had similar demographic characteristics. The mean age of case-patients was 25·7 years [standard deviation (S.D.) = 11·5, range 15–70 years], compared to a mean of 25·6 years (S.D. = 10·7, range 14–68 years) in controls. Thirty-one (48%) cases were male, compared to 62 (48%) in the control group. Forty-seven (73%) case-patients and their matched controls lived in urban districts, the remainder resided in rural areas of Diyarbakir or its surroundings.

The following risk factors were significantly associated with typhoid fever in univariate analysis: living in a crowded household, consuming beverages or water outside the home, eating outside the home, and eating raw leafy vegetables (Table 1). Notably, number of toilets per household and washing hands before eating were not associated with typhoid fever.

The following variables were considered in the multivariate analysis: living in a crowded household, consumption of beverages or water outside the home, eating outside the home, eating raw leafy vegetables (lettuce with *cig kofte*, lettuce alone, green salad, vegetables with kebab). The result of the multivariate analysis (Table 2) showed that living in a crowded household (OR 3·31, 95% CI 1·58–6·92, $P = 0·002$), eating *cig kofte* (OR 6·45, 95% CI 2·56–16·28, $P = 0·000$) and eating lettuce salad (OR 3·31, 95% CI 1·38–7·94, $P = 0·007$) were independently associated with typhoid fever in this study population.

Table 2. *Multivariate analysis using conditional logistic regression of risk factors for typhoid fever in Diyarbakir, Turkey*

Risk factor	OR	95% CI	*P* value
Living in a crowded household	3·31	1·58–6·92	0·002
Consumption of beverages or water outside home	1·16	0·55–2·42	0·701
Eating risky foods outside home			
Lettuce with *cig kofte*	6·45	2·56–16·23	0·000
Lettuce salad	3·31	1·38–7·94	0·007
Green salad	2·16	0·70–6·72	0·182
Salad with kebab	0·81	0·24–2·74	0·728
Eating outside home	1·07	0·36–3·20	0·900

OR, Odds ratio; CI, confidence interval.

DISCUSSION

The main finding of this study was that consumption of leafy vegetables, including *cig kofte*, a traditional

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food, was a significant risk factor for typhoid fever among adults in southeast Turkey. *Cig kofte* (raw meatballs) is made of spices, ground meat, and boiled or pounded wheat. It is uncooked and eaten with lettuce leaves or lettuce salad. It is a popular dish, eaten in the home and sold on roadside cabins and in restaurants, thus exposing a large segment of the population to lettuce.

Identification of lettuce consumption as a risk helped to support the hypothesis that local plantation vegetables grown in soil irrigated with contaminated sewage water contributes to the endemicity of *S. typhi* in the region. The high rectal carriage rates of *S. typhi* amongst workers at the plantation near Diyarbakir [17] is also consistent with this. Sewage water from the city is used to irrigate this plantation. Vegetables (especially lettuce) from the plantation are distributed within Diyarbakir and the surrounding area. Furthermore, molecular typing demonstrated close relatedness between *S. typhi* strains cultured from plantation lettuce and those from clinical isolates [18].

Our findings emphasize the importance of local epidemiology in endemic typhoid fever. This is evident in other studies. Eating ice cream as well as food from a roadside cabin during the summer months was associated with typhoid fever in a study from Karachi, Pakistan [12]. An Indonesian study found ice cubes to be an important source [19]. In this study, household factors were also significant, including food sharing, lack of soap, and lack of toilets [19]. In another study from Indonesia, consumption of food bought from street vendors was an important risk factor [11].

In contrast to outbreaks of typhoid fever where contaminated drinking water was reported to be a source [20], we did not find drinking water in the home to be an independent risk factor. Consumption of water outside the home was associated with typhoid fever in univariate analysis, but this variable was not in our multivariate model. Possibly, home drinking water was contaminated, but may not have contained a sufficient number of bacteria to cause infection in our semi-immune population. Evidence exists that contaminated food tends to have higher concentration of *S. typhi* than water [21]. A study of endemic typhoid fever in Santiago also failed to detect an association between a water source and typhoid fever [9].

In addition to lettuce, we found crowding to increase the risk of typhoid fever. This probably represents a greater 'opportunity' for person-to-person transmission within households. Reported adherence to hand washing was similar between cases and controls in our study. Previous studies however have demonstrated an association between poor hygiene and carriers of *S. typhi* in families with children who had typhoid fever [22]. In an Indonesian study, poor hygiene was found to be a risk factor for typhoid fever [23]: washing hands before eating was an important preventive measure. In other Indonesian studies, lack of soap for hand washing was independently associated with typhoid fever [11, 19].

In conclusion, consumption of raw leafy vegetables increased the risk of typhoid fever in Diyarbakir, Turkey. Crowded household conditions also increased the risk. Typhoid fever remains an important public health problem in Turkey.

DECLARATION OF INTEREST

None.

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