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Risk factors of acute diarrhoea in summer – a nation-wide French case-control study

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SUMMARY

The aim of this study was to identify risk factors for acute diarrhoea (AD) during the summer in France. A matched case-control study was conducted at a national level among patients of 500 general practitioners (GPs). From July to September 1996, 468 case-control pairs were included. Cases were more likely than controls (i) to live away from their main residence (OR 3·0; 95% CI 1·6–5·7), (ii) to have returned from a country at high risk of AD (OR 4·6; CI 0·9–23·1), and (iii) to have been in contact with a case of AD (OR 2·0; CI 1·3–3·1). A significantly decreased risk of AD was found for consumption of well-cooked chicken (OR 0·5; CI 0·3–0·8) and raw or undercooked home-made egg-containing products (OR 0·6; CI 0·4–0·8). These findings suggest that travel to high-risk areas, or travel within France, and being in contact with a case of AD, are risk factors for the occurrence of AD in summer in France.

INTRODUCTION

Acute diarrhoea (AD) substantially affects the developed countries population [1, 2]. In the United States, it is the second most common short-term disease after acute upper respiratory illnesses [1]. Although not usually considered to be life-threatening, AD has an important social and economic impact [1, 3–6].

In France, data on AD are collected continuously from a national sample of sentinel general practitioners (GPs) [7]. According to this ongoing surveillance system, which was initiated in 1991, approx. 2% of the French population (i.e. 63 cases/1000 inhabitants per year) consult a GP for AD each year [8]. A seasonal pattern is observed, with a peak in winter and an increasing number of cases reported in summer, as stated by a periodic regression model [9].

Most reports dealing with the epidemiology of AD in industrialized countries concern diarrhoea caused by particular pathogens. However, AD can be caused by a variety of factors other than microbiological pathogens including toxins, drugs, congenital diseases, physiological disorders, allergens or food intolerance. Transmission can be through person-to-person contact, contact with animals, environmental exposures, consumption of contaminated water or consumption of a wide range of foods. Public health interventions may be envisioned against these non-infectious causes of AD and their transmission route. Thus, determination of the risk of AD associated with these factors is of great interest. In addition previous studies on the epidemiology of AD have addressed single outbreaks. Few community studies have been reported [1, 2]. Community-based observational studies using a non-discriminatory case definition have the advantage to explore AD acquired through exposure to a wide range of risk factors. They are needed to identify gross and non-specific risk factors that may

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affect the occurrence of the disease on a large scale. In a previous study, we investigated the winter peak [9]. The objectives of the present study were to identify risk factors associated with AD during the summer.

We postulated that at the community level, the risk factors for AD in summer included food vehicles of common foodborne organisms, i.e. raw and undercooked meat [10, 11], undercooked chicken [12, 13], egg products [14–16], raw milk products [17, 18] and raw shellfish [19]. Because of the increase in the number of cases of AD during the summer, frequent summer activities such as travelling [20] and swimming [21] were investigated. Prior contact with a case of AD [22], or prior use of prescription drugs [23, 24], which were found to be independent risk factors for AD in winter [9], were also considered. All the above factors were investigated in a case-control study of patients in a general practice setting.

METHODS

Case selection

This study was conducted at a national level among patients of 500 GPs who participate in the ongoing sentinel surveillance of AD in France. These GPs account for about one percent of the total number of French GPs [7]. A case was defined as a person consulting a GP of the sentinel network for AD that had started during the past 14 days. Controls were patients consulting the GP for non-gastrointestinal diseases. During the period July–September 1996, all 500 sentinel GPs were asked to enroll in the study (i) the first case of AD identified each month, and (ii) a control matched to the included case for age (i.e. in the age groups 0–4, 5–14, 15–59, or > 60 years), month of consultation (i.e. interview) and GP. Assuming an exposure rate of 10% among controls, a two-tailed level of significance of 5% and a power level of 80%, the enrolment of 278 patients was expected to permit detection of a minimal odds ratio (OR) of 2 [25].

Data collection

Informed consent to participate in the study was obtained from cases and matched controls, who were then interviewed by the GPs, using a standardized questionnaire. The clinical features of AD were noted for each case, especially fever, and blood or mucus in the stools. Data on food consumption, travel history, swimming, exposure to a subject with AD illness, and prior use of antibiotic or gastric acid antisecretory drugs, were collected for both cases and controls. During the 10 days before the interview, exposure to the following foods was explored: beef, chicken, raw milk products, home-made products containing raw or undercooked eggs, and raw shellfish. For beef and chicken, the cooking status was asked (undercooked or well-cooked). Meat was considered undercooked if it was still at all pink after cooking. Home-made products containing raw or undercooked eggs included mayonnaise, custard, sauces and chocolate mousse. Information was obtained about the type of shellfish consumed among those who consumed raw shellfish. To determine travel history, all participants were asked whether they were living away from their main residence at the time of the interview (i.e. travelling in France), or whether they had travelled abroad during the preceding month. Those living away from their main residence were asked to state whether they were on full or partial board, i.e. having at least one meal a day in a restaurant. Foreign destinations were classified according to the risk of acquiring diarrhoea [20]. Areas considered at high risk were Latin America, Africa and Asia. Histories of swimming in various recreational waters (sea, lake, swimming pool, or river) were explored during the 10 days before the interview.

Laboratory investigations and acute diarrhoea management

As this study was nested in an ongoing surveillance of AD in each GP's practice, no systematic laboratory investigations were conducted. A search for pathogens in stools was only performed when requested by the GP. GPs were asked whether they had (i) prescribed drugs, (ii) prescribed sick leave or (iii) referred cases to hospitals.

Eligibility criteria

During the 3-month study period, 253 GPs belonging to the national sentinel network (50·6%) participated in the study and included 487 case-control pairs. All the questionnaires were reviewed by the main investigator (Y.Y.) who checked the eligibility criteria and the precision accuracy of case-control matching. Five cases that had AD for more than 15 days prior to the interview and 14 controls who had gastrointestinal clinical manifestations within 3 months prior to the

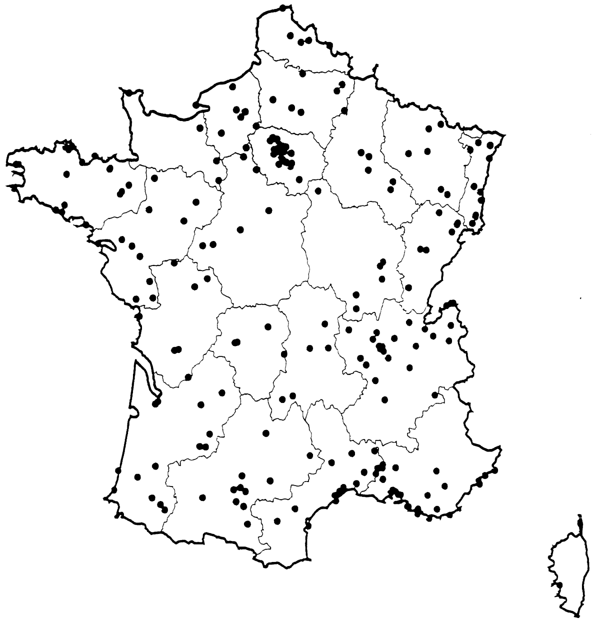

Fig. 1. Geographical distribution of cases of acute diarrhoea in France, July–September 1996. Each dot represents 1–3 cases included in the present case-control study.

Table 1. *Characteristics of 468 cases of acute diarrhoea reported in France, July–September 1996*

Variables	*n* (%)
Age	
< 5 years	58 (12·4)
5–14 years	57 (12·2)
15–59 years	290 (61·9)
> 59 years	63 (13·5)
Month of enrolment	
July	144 (30·8)
August	154 (32·9)
September	170 (36·3)
Sex	
Female	237 (50·6)
Male	231 (49·4)
Place of residence	
Rural	217 (46·4)
Urban	251 (53·6)

interview were excluded for failure to meet the eligibility criteria. If either member of a pair of case patients and control subjects did not meet these criteria, the pair was excluded. After these exclusions, a total of 468 case-control pairs was included in the analysis (Fig. 1).

Data were collected and stored with the approval of the French national committee for computerized records and freedoms.

Statistical analysis

Mac Nemar's chi-square test and Wilcoxon rank-sum test for paired data were used to compare the unmatched general characteristics of cases and controls.

The crude disease-exposure association was determined by estimating the OR and its 95% confidence interval (CI). This was done by univariate conditional logistic regression, to account for the matched design. The significance of the OR was assessed by the Wald test [26].

Data were stratified on matched variables, to check for modifications in the association between AD and the different types of exposure. The Breslow–Day homogeneity test was performed to evaluate the heterogeneity of the OR within strata [26].

Exposures for which the *P*-value was less than 0·25 in univariate analysis, and matched variables for which a significant difference was found between cases and controls ($P < 0{\cdot}05$), were submitted to a multivariate conditional logistic regression model. Backward stepwise regression procedures were used to develop the final multivariate model and possible interactions were examined [27]. The fit of the model was assessed by the logistic regression diagnostics procedure [28].

A *P* value of less than 0·05 (two-tailed) was considered significant. Statistical analysis was carried out with SAS 6.11 software (SAS institute Inc. Cary, NC, USA).

RESULTS

Sociodemographic and clinical characteristics

The baseline characteristics of the cases are shown in Table 1. As cases and controls were matched for age group, month of interview and GP, the respective distributions of these variables were not different. Cases and controls did not differ in regard to sex and place of residence. However, when age was considered as a continuous variable, the controls were older than the cases (median 32, range 1 month–91 years *vs.* median 29 years, range 2 months–88 years, $P = 0{\cdot}0001$). Controls were included on average 2 days after the cases to which they were matched.

Of the 468 cases of AD, 194 (41·5%) reported fever, 299 (63·9%) nausea or vomiting and 410 (87·6%) abdominal pain. AD had lasted for less than 1–14 days (median 2 days) at the time of the interview. The

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Table 2. *Cases of acute diarrhoea and matched controls by type of exposure, France, July–September 1996*

Variables	Cases ($n = 468$) No. (%)	Controls ($n = 468$) No. (%)	Unadjusted matched OR (95% confidence interval)	*P*-value
Beef meat*†				
None	94 (20·1)	85 (18·2)	1·0	
Undercooked	110 (23·5)	112 (23·9)	0·9 (0·6–1·6)	0·40
Well cooked	260 (55·6)	265 (56·6)	0·9 (0·6–1·2)	0·44
Chicken*†				
None	122 (26·1)	73 (15·6)	1·0	
Undercooked	15 (3·2)	7 (1·5)	1·2 (0·4–3·2)	0·78
Well cooked	325 (69·4)	381 (81·4)	0·4 (0·3–0·6)	0·0001
Raw milk products*	110 (23·5)	115 (24·6)	0·9 (0·6–1·3)	0·64
Raw or undercooked egg-containing products*	158 (33·8)	198 (42·3)	0·6 (0·5–0·9)	0·005
Raw shellfish†‡				
None	426 (91·0)	432 (92·3)	1·0	
Oysters	24 (5·1)	24 (5·1)	0·9 (0·5–1·9)	0·85
Mussels	20 (4·3)	13 (2·8)	2·3 (0·9–5·4)	0·06
Cockles	4 (0·9)	6 (1·3)	0·7 (0·2–3·3)	0·65
Clams	3 (0·6)	6 (1·3)	0·6 (0·1–1·3)	0·08
Living away from one's main residence§	73 (15·6)	30 (6·4)	3·7 (2·1–6·4)	0·0001
Travelling abroad‖¶				
No	430 (91·9)	440 (94·0)	1·0	
Low risk areas	5 (1·1)	10 (2·1)	0·4 (0·1–1·4)	0·18
Intermediate risk areas	20 (4·2)	14 (3·0)	1·6 (0·8–3·2)	0·21
High risk areas	13 (2·8)	4 (0·9)	3·5 (1·1–10·7)	0·03
Swimming*	152 (32·5)	145 (31·0)	1·1 (0·8–1·6)	0·46
Contact with a case of acute diarrhoea*	103 (22·0)	47 (10·0)	2·7 (1·8–4·0)	0·0001
Prior use of antibiotics‖	39 (8·3)	45 (9·6)	0·9 (0·5–1·3)	0·49
Prior use of gastric acid antisecretory‖	8 (1·7)	7 (1·5)	1·2 (0·4–3·5)	0·78

* During the 10 days before interview.
† Data per cases and controls may not sum to 468 because of missing data.
‡ Data may not sum to 468 because cases or controls may have consumed more than one type of shellfish.
§ At the time of interview.
‖ During the 30 days before interview.
¶ Low-risk areas: North America, Northern and Central Europe, Australia and New Zealand; intermediate-risk areas: Caribbean, Northern Mediterranean, Israel, Japan and South Africa; high-risk areas: Latin America, Africa and Asia.

number of stools per day was 1–30 (median 5 stools/day). Blood and mucous were respectively reported in the stools of 4 (0·9%) and 43 cases (9·2%).

The 468 controls consulted the GPs for 103 different illnesses and symptoms.

Factors associated with acute diarrhoea

Compared to the controls, the cases were more likely to live away from their main residence at the time of the interview, to have returned during the 30 days before the interview from a country at high risk of acute diarrhoea, or to have been in contact with a case of AD during the 10 days before the interview (Table 2). When such contact had occurred AD had developed 0–10 days thereafter (median 2 days). None of the foodstuffs tested was found to be a risk factor for AD. A significantly decreased risk of AD was observed for consumption of well-cooked chicken and raw or undercooked home-made egg-containing products. There was no significant association between AD and swimming, travel abroad in areas where the risk of AD was low or intermediate, and prior use of antibiotic or gastric acid antisecretory drugs.

When living away from one's main residence, the risk of AD was greater among subjects who reported full or partial board than among those who did not (n [%] of cases 16 [21·9], n [%] of controls 2 [6·7], OR 8·0, CI 1·8–34·8).

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Table 3. *Acute diarrhoea and history of prior contact according to age, France, July–September 1996*

Contact with a case of acute diarrhoea*	Cases ($n = 468$) No. (%)	Controls ($n = 468$) No. (%)	Unadjusted OR (95% confidence interval)	P-value
< 5 years	17 (3·6)	3 (0·6)	8·0 (2·2–28·7)	0·001
5–14 years	12 (2·6)	6 (1·3)	2·2 (0·8–6·3)	0·15
15–59 years	70 (15·0)	31 (6·6)	2·6 (1·7–4·1)	0·001
> 59 years	4 (0·8)	7 (1·5)	0·6 (0·2–2·2)	0·43

* Breslow–Day test for homogeneity of the odds ratios, $P = 0·04$.

Table 4. *Multivariate estimates of risk for factors associated with acute diarrhoea, France, July–September 1996*

Variables	OR (95% CI)	P-value
Living away from one's main residence*	3·0 (1·6–5·7)	0·001
Travelling abroad to high risk areas†‡	4·6 (0·9–23·1)	0·06
Contact with a case of acute diarrhoea§	2·0 (1·3–3·1)	0·002
Well cooked chicken§	0·5 (0·3–0·8)	0·002
Raw or undercooked egg-containing products§	0·6 (0·4–0·8)	0·003

* At the time of interview.
† During the 30 days before interview.
‡ High risk areas: Latin America, Africa and Asia.
§ Ingested during the 10 days before interview.

When subjects were stratified for age group, the association between AD and a history of contact with a case of AD was not constant in all age groups (Table 3). This association was strongest among children below 5 years of age.

Age, whose distribution as a continuous variable was different in the cases and controls, was kept in the final multivariate model. This model identified four factors independently associated with AD (Table 4): living away from one's main residence and contact with a case of AD as risk factors, and consumption of well cooked chicken and raw or undercooked home-made egg-containing products as potential protective factors. Travel in high risk areas, even though not significantly associated with AD, was not excluded from the model because of the high value of the OR's point estimate. A history of full or partial board during travel was not included in the multivariate model because it was only reported for cases and controls living away from their main residence. Interaction between prior contact with a case of AD and age was not included in this model because it was not statistically significant on inclusion in the final model ($P = 0·09$). The logistic regression diagnostics procedure showed that the entire set of covariate patterns was correctly fitted by the final model.

Laboratory investigations and acute diarrhoea management

Stool cultures were performed in 32 cases (6·8%). A pathogen was found in 13 of these cases (40·6%) as follows: *Salmonella* sp. ($n = 9$), *Campylobacter jejuni* ($n = 2$), *Shigella* sp. ($n = 1$) and *Clostridium difficile* ($n = 1$). GPs prescribed drugs in 453/468 (96·8%) cases of AD (median number prescribed per case 2, range 0–5). One hundred and eight cases (23·1%) were asked by the GP to stay home from work. The median period of sick leave prescribed was 3 days (range 1–12). Two cases (0·4%) were referred to hospital.

Risk of invasive acute diarrhoea and consumption of raw or undercooked home-made egg-containing products

We performed a specific analysis restricted to a subset of cases with reported fever and blood or mucus in stools, and their matched controls (i.e. $n = 23$ pairs). Its purpose was to confirm the expected role of consumption of raw or undercooked egg-containing products in the occurrence of invasive acute diarrhoea, which is often associated with bacterial enteric infections. The estimated crude matched OR was 2·3 (CI 0·6–9·0). In the complementary subset of cases with non-invasive acute diarrhoea and their matched controls (i.e. $n = 445$ pairs) the estimated crude matched OR was 0·6 (CI 0·4–0·8).

DISCUSSION

The results of this French case-control study suggest that travelling to a country at high risk of AD, or even travel within France, and being in contact with a case of diarrhoea, were independent risk factors for AD in summer. They also suggested that, at least in this study, consumption of well cooked chicken and products containing raw or undercooked eggs may have been independent protective factors for AD.

Although approx. 49% of the sentinel GPs did not participate in the study, this was unlikely to have introduced a selection bias as these non-participants included neither cases nor controls. In this study a non-discriminatory case definition was used because the protocol was designed to identify the most gross and non-specific risk factors of AD on a large scale. As a result, the effects of agent specific risk factors were diluted out by the inclusion of cases whose diseases were caused by other agents and who may be considered to be controls for those agents. A case was defined as person consulting a GP of the sentinel network for an AD that had started during the past 14 days. AD was not further defined and it was left up to the physician. However, 91% of the cases included in this study had three or more stools within 24 h and for periods of less than 14 days, thus fulfilling the World Health Organisation's definition of acute diarrhoea [29]. The control patients were selected from general practice and not from the general population. Nevertheless, selection bias was unlikely, because of the wide variety of reasons for encounter among the controls. Recall bias was also not likely, because information concerning most types of exposure considered was requested for 10 days prior to the interview. Bias was probably not introduced by the interviewers' knowledge of the hypothesis being tested; thus, raw or undercooked home-made egg-containing products were not positively associated with illness, as might have been expected if bias had occurred.

The increasing risk of AD among those travelling to high-risk areas has been stressed in the past. Previous authors estimate that between 20 and 50% of people who travel from industrialized countries to the developing world experience acute diarrhoea during travel or soon after returning home [20, 30, 31].

Acute diarrhoea has been reported in people from low risk areas travelling to another low risk area [30]. However, to our knowledge, no epidemiological study has been conducted to assess the risk of AD among citizens of industrialized countries who travel in their homeland. In this study, although controls were patients consulting the GP for a wide variety of reasons, 18% were patients with a chronic disease. Therefore, we can postulate that our finding is due to the fact that controls with a chronic disease may travel less often than cases. However, even after restricting our analysis to controls without chronic disease and their matched cases, we found that travelling in France was associated with AD. The OR was unchanged when compared to the initial analysis. We can also hypothesize that people who are travelling away from home are more likely to seek medical attention in response to AD than those living at home. However, on the other hand, we may also expect that those living at home would consult more quickly a GP than those travelling away from home; it is easier for a patient to see his usual GP with whom he has already created a patient–physician relationship.

In our study, the strong association between full or partial board and AD among those who travel suggests that food intake may contribute to the development of AD. Although the development of national standards has improved food safety in industrialized countries, the scale of foodborne transmission is increasing, and new hazards are being identified [32]. Because of changes in their living conditions and behaviour, travellers, even those travelling in industrialized countries, are probably more often exposed to such hazards. In particular, travellers eat often in restaurants, and cafeterias, and buy food from street vendors. In 52% of the 2397 outbreaks of foodborne disease reported to the United States Centers for Disease Control between 1983 and 1987, the food incriminated was prepared by a restaurant, delicatessen shop or cafeteria [33].

Contact between subjects is known to provide opportunities for transmission of various enteric pathogens [22]. However, in the present estimate of the median interval between contact and the development of AD symptoms, person-to-person transmission and shared exposure to contaminated food could not be formally differentiated.

In this study, controls were more likely than cases to have eaten well-cooked chicken. Poultry is known to be an important reservoir of organisms involved in the occurrence of AD, especially *Salmonella* sp. and

Campylobacter sp. [12, 34–36]. It was therefore reasonable to expect that in our study well-cooked chicken would have a protective effect, because thorough cooking of a highly contaminated food can prevent the occurrence of the disease in which this food is involved.

Our results suggested that consumption of raw or undercooked home-made egg-containing products may have been an independent protective factor for AD, which is paradoxical in view of what was expected. However, in earlier studies, raw or undercooked egg products have been implicated as vehicles of invasive AD due to *Salmonella* sp. [14–16]. Unlike the authors of these studies, we investigated all the clinical features of AD, and not only invasive AD due to *Salmonella* sp. When we restricted our analysis to invasive AD we found a positive association between raw or undercooked egg-containing products and invasive AD and the strength of this association was consistent with the associations reported in the past for sporadic cases of salmonellosis [14, 16, 37].

Although the effect of raw or undercooked home-made egg-containing products has not been explored among patients presenting all the clinical features of AD, we must be cautious regarding this specific result. First, we found an opposite result to our prior hypothesis. Second, the possibility of a bias cannot be completely excluded. In particular, in this study we can hypothesize that we have enrolled cases with AD caused by agents associated with egg consumption, but also cases with AD caused by agents not associated with eggs and acquiring infection through the consumption of unidentified non-egg dishes. If among the cases included, the proportion of AD caused by agents not associated with eggs was greater than the proportion of AD caused by agents associated with eggs, we might expect that more cases were likely to be eating non-egg dishes. As a result, we may expect a greater proportion of controls eating raw or undercooked containing dishes. The methodology we used and especially the non-discriminatory case definition may therefore give rise to misidentification of protective effects. Finally, the biological basis of this observation is unknown. We may postulate that eggs contain substances capable of preventing AD, and that chicken immunoglobulins, which are actively secreted into egg yolks [38, 39] are capable of neutralizing human infections due to microbiological agents involved in non-invasive AD, but these possibilities require further epidemiological and laboratory studies to confirm these findings.

In summary, in this French study, travel to a country at high risk of AD, and prior contact with a case of AD, were found to be the risk factors for AD in summer in France. In addition, travel in France was found to be a main risk factor for the occurrence of AD. To our knowledge, this is the first time that an epidemiological study assesses the risk of AD among citizens of industrialized countries who travel in their homeland. Preventive measures should therefore be strengthened, and travellers should be aware of the risk of diarrhoea, even when travelling through their homeland. Restaurants, cafeterias and street vendors, more frequently patronized during the summer, should be meticulously inspected for standards of hygiene. Travellers to developing countries must be repeatedly instructed about food and beverage preparation, immunization and prophylactic antimicrobial drugs. Lastly, breaks in proper hygiene must be avoided, to prevent person-to-person transmission.

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