The use of the case-crossover design in a continuous common source food-borne outbreak

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SUMMARY

When applicable, case-crossover studies may be quicker and cheaper to complete than case-control studies. Because time is a major issue in outbreak investigations, we evaluated the interest of this design during a continuous common source food-borne outbreak of salmonellosis for which the vehicle (hamburgers) was also implicated by environmental and laboratory investigations. Seventeen of the 35 cases identified in the outbreak were included in the study according to the availability of menu records with detailed information on food consumed at each meal. Food exposures during a 3-day risk period before onset of illness were compared to those of a control time-interval of the same duration that preceded the risk period by two days. Seventy-seven per cent of the cases (13/17) had consumed hamburgers in the three days preceding onset of illness compared with 29 % (5/17) during the control period ($P = 0.04$, odds ratio = 5, 95 % CI: 1·1–46·9). In this investigation the case-crossover design proved to be a useful and efficient alternative to the case-control approach. However, further evaluation of this design in outbreak investigation is needed.

INTRODUCTION

The aim of investigations of food-borne outbreaks is to identify the vehicle and the source of infection in a timely way so that appropriate control measures can be implemented rapidly. The investigation relies on descriptive epidemiology to generate hypotheses and on an analytical study, usually a case-control design complemented by an environmental and laboratory enquiry [1]. However, most food-borne outbreaks, particularly when they are related to a particular meal, have an implied hypothesis, thus, the analytical study can be implemented as soon as the outbreak is recognized. Selecting and interviewing controls is time consuming and may be difficult and sometimes not possible [2]. Therefore, any alternative approach to the case-control design that would save time needs to be considered and evaluated.

The case-crossover design, first described by Malcolm Maclure in 1991 [3], compares in the same person, exposure to the risk factors just before the onset of disease during a time interval before the onset of illness (the risk period) to a time interval of the same duration prior to the risk period (control period). This study design does not require the time consuming process of selecting and interviewing controls. As for matched studies, only pairs of periods discordant for the exposure of interest are used to calculate the odds ratio (OR).

We used the case-crossover design as part of the investigation to identify the food vehicle during a *Salmonella* Typhimurium outbreak that affected mostly elderly persons in several care facilities in France. The food vehicle was also implicated by environmental and laboratory investigations [4].
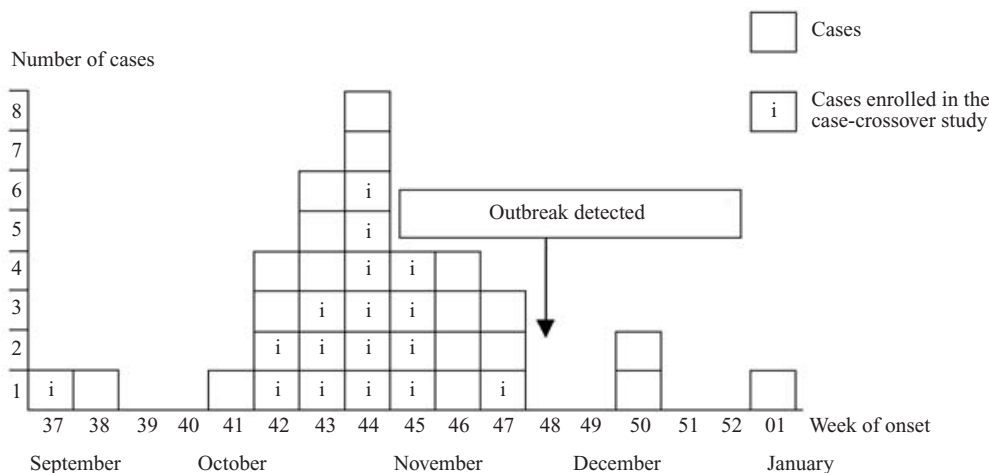
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Fig. 1. Cases of *Salmonella* Typhimurium by week of onset, France 1999–2000.

BACKGROUND

The outbreak occurred between 15 September 1999 and 7 January 2000, in the Alpes de Haute-Provence district (Fig. 1). Thirty-five case-patients, all confirmed by positive stool or blood cultures, were identified. Twenty-nine (83%) had occurred in six care institutions (hospitals or retirement homes) and the remaining six cases amongst children and adolescents who had not been in contact with hospitals. Of the 29 cases identified from care institutions, 25 (86%) were patients who had been admitted for several days or weeks at the time of onset and four cases were health-workers from the same care institutions. Three patients (8·6%) who had severe underlying conditions died. Amongst patients from care institutions, the most common food exposure was the consumption of hamburgers. The investigation into the food chains of the care institutions affected by the outbreak showed that the hamburgers consumed were frozen and came from a single producer. The six cases unrelated to a care institution were children and adolescents who, in the three days prior to onset, had eaten in school canteens that served hamburgers supplied by the same producer as the care institutions. *Salmonella* Typhimurium was cultured from two of the five batches of hamburgers seized from various hospitals and school canteens. All food and patients isolates belonged to lysotype definitive type 104, exhibited the same resistance phenotype ACSSuT and the same DNA macrorestriction profile (pattern) [4].

METHODS

To test the hypothesis that the consumption of hamburgers during the three days prior to onset of
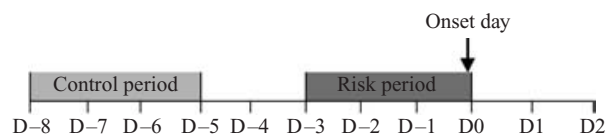

Fig. 2. Risk and control periods in relation to date of onset. Case-crossover study of a *Salmonella* Typhimurium outbreak, France 1999–2000.

disease was the source of *Salmonella* Typhimurium infection in this outbreak, we conducted a case-crossover study among in-care case-patients for whom complete records of the foods consumed at each meal were available. The study was done as part of the investigation at the same time as the environmental and microbial investigation and before the results of the hamburger cultures were known.

The risk period was defined as the three days preceding the date of onset of illness. We chose a control period of the same duration that preceded the risk period by two days (Fig. 2). Case-patients who had been admitted for less than 8 days were not included. For meals eaten during the risk and control period we attempted to retrieve the various meats and meat products consumed by case-patients from available menus. The information on meat and meat products consumed during each meal of the two periods could be retrieved for 17 (68% patients). The relative risk for each meat product was estimated by calculating the Mantel-Haenszel OR for matched pairs and it's 95% confidence interval (CI) [3].

RESULTS

Seventeen in-care case-patients (68%) with a median age of 76 years (range: 6–92), a male to female sex

Table 1. *Food exposures during risk and control periods, case-crossover study of a* Salmonella Typhimurium *outbreak, France 1999–2000*

Foods	Eaten during the risk period (n = 17)		Eaten during the control period (n = 17)		Discordant pairs exposed in		OR	95 % CI	P
	n	%	n	%	Risk period	Control period			
Veal	5	29·4	1	5·8	5	1	5	0·6–236·5	0·2
Pork	4	23·5	6	35·3	3	5	0·6	0·1–3·1	0·7
Hamburgers	13	76·5	5	29·4	10	2	5	1·1–46·9	0·04
Ham	6	35·3	5	29·4	3	2	1·5	0·2–17·9	1
Pâté	2	12·0	2	12·0	1	1	1	0·01–78·5	0·5
Chicken	2	12·0	3	17·6	1	2	1	0·01–78·5	0·5
Turkey	11	64·7	6	35·3	8	3	2·7	0·7–15·6	0·2
'Cordon bleu'	0	0·0	2	12·0	0	1	0	—	0·5
Lamb sausages	2	12·0	0	0·0	2	0	—	—	0·5
Chicken sausages	2	12·0	0	0·0	2	0	—	—	0·5

ratio of 0·7 and a median date of onset of 3 November 1999 (range: 15 September 1999 to 24 November 1999) were enrolled in the case-crossover study (Fig. 1). Seventy-seven per cent of the cases (13/17) had consumed hamburgers in the three days preceding onset of illness compared with 29 % (5/17) during the control period ($P = 0.04$). These results indicate that during the outbreak period, consuming hamburgers in any of these care institutions increased five time the risk of *Salmonella* Typhimurium infection in the following three days (OR = 5, 95 % CI: 1·1–46·9). There was no evidence of an association between the consumption of other meats and the disease (Table 1).

DISCUSSION

To our knowledge, the use of the case-crossover design in the investigation of food-borne outbreaks has not been reported before. The method has been applied to the study of transient exposures such as drug adverse events [5, 6], of air pollution on mortality [7–9], the effect of cellular telephones on motor vehicle accident [10] and of heavy physical activities on myocardial infarction [11]. It was also used to study risk factors of haemorrhagic fever with renal syndrome and gave similar results as a concurrent case-control study [12].

In this outbreak, this design proved to be a useful and efficient alternative to the case-control approach. This particular outbreak investigation had been initiated with some delay [4]. Thus, we sought for an alternative to a case-control design in order to avoid possible information and selection biases, especially

as most patients were very old, had severe underlying conditions and were very difficult to interview [4]. Furthermore, matching controls for the severity of underlying conditions would have been necessary but difficult to achieve. Consequently, since each case was his own control, the case-crossover method allowed a very good matching on patient's susceptibility. This design was also easy to implement because exposures to foods were documented precisely, by days and meals, in most of the in-care patient's records.

However, case-crossover studies are also subject to biases [13]. The control exposure should be representative of the expected distribution of exposure for follow-up times that do not result in a case. The choice of the control period is therefore essential and poses specific problems depending on the subject [9]. By separating the risk and the control period by a two day-interval we tried to take into account the fact that some foods are often consumed once weekly: if the control period was just before the risk period the relative risk could have been falsely over-estimated.

In our study we obtained information on food consumption from an administrative source and thus could not be sure of what the patients had actually eaten. Hamburgers are often proposed as an alternative to other meats, particularly when patients have difficulties eating solid foods. Therefore, miss-classification errors of the exposure to hamburgers may have occurred. However, there is no reason to think that these errors would have affected differently the risk and the control periods.

Some of the case-patients who had onset prior to the 8th day of admission or for whom food information

could not be retrieved from menu records were not included. Patients included were, therefore, not representative of all cases, in particular, they tended to have stayed longer in the institutions than those excluded. In addition, because we did not enrolled a control group, we could not compare the results of the case-crossover study to a concurrent case control approach and therefore evaluate the case-crossover design in an epidemiological way. However, the concordance between the results of the case-crossover study and the environmental and microbiological investigations is not in favor of a fallacious association. In this outbreak, characterized by a continuous and long lasting common food source, we concluded that the case-crossover design was a valid, discriminative and time saving method to identify the food vehicle.

The use of this design in this particular outbreak highlights the limited circumstances where it might be useful. The method appears to be most applicable to an institutional setting where independent routine documentation of exposures is available. Thus, as in this outbreak, food exposures can be assembled without worrying about the loss of information due to differential recall over time. This design is of particular potential interest in settings such as hospitals, long term care facilities, nursing home and haemodialysis centre where nosocomial outbreaks occurred quite frequently and where many of the exposures of interest are documented in patient records and files.

For food-borne outbreaks that occur in populations such as infants, elderly or mentally deficient this design needs also to be considered because finding controls is extremely difficult and the foods consumed are usually documented in records. However, it may not be appropriate in many outbreak settings. For common meal food-borne outbreaks, which are the most frequent, an appropriate control period is not available since the population at risk is defined as those who shared the same meal, during the time-interval corresponding to the incubation period. In a point source outbreak of a widely distributed food this design would also not be appropriate for the same reason. Additionally, if the contamination of the product was a single event in one lot of food, the food may not be implicated because the foodstuffs, independent of the specific contaminated batch, would be eaten in both case and control periods. The case-crossover design may be also difficult to use in outbreak investigations if precise (discrete) dates of exposure are not available, if investigators rely on the memory of patients, particularly when the incubation period is long. An appropriate control period would also be difficult to define if exposure changes systematically over time.

An additional concern needs to be considered if this study design is used based on case recall only. There would be a bias towards better remembering foods eaten recently than foods eaten earlier. Therefore, a spurious association could arise, as a result of a food item being better memorable during the period at risk than the control period, rather than contaminated. In such situations, the method would need to be validated by including a control group to assess this potential bias. The method also requires that the incubation period is well known and can be used to define a reasonable exposure window. Unfortunately the incubation periods for some food-borne agents, such as listeriosis or trichinellosis, may be quite long and variable which would alter the efficiency of the method. Therefore, one needs to take into account as precisely as possible the distribution of the incubation period of the agent to define the risk and control period. In our example we choose a risk and control period of 3 days, an incubation period that is well accepted for salmonellosis. However, a longer incubation (median 72 h with a range of 12–120 h) has been reported during two prolonged common source community-wide outbreaks of salmonellosis associated with eating uncooked tomatoes [14]. The use of our case-crossover design with a 3 days at risk period in these two outbreak would have resulted in miss-classification of the exposure, with less case-patients falling in the period at risk and more in the control period, which would have biased the results towards the nil.

There are certainly many outbreaks that occur in institutional settings that never get investigated because of constraints on patient's memory, costs of investigation and other reasons. The case-crossover method may provide a way to increase the likelihood of successfully investigating these outbreaks. However, because of the numerous questions discussed above, further evaluation of the use of the case-crossover design in outbreak investigations is still needed.

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REFERENCES

1. Goodman RA, Buehler JW, Koplan JP. The epidemiologic field investigation: science and judgment in public health practice. Am J Epidemiol 1990; **132**: 9–16.

2. McCarthy N, Giesecke J. Case–Case comparisons to study causation of common infectious diseases. Int J Epidemiol 1999; **28**: 764–768.

3. Maclure M. The case cross over design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991; **133**: 144–153.

4. Haeghebaert S, Duché L, Massini B, et al. Epidémie de salmonellose à Salmonellose à Salmonella Enterica sérotype Typhimurium dans les institutions médico-sociales, Alpes de Hautes-Provence, Septembre 1999–Janvier 2000. Bull Epidemiol Hebd 2000; **36**: 153–155.

5. Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of adverse events from diphteria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 1995; **345**: 567–569.

6. Confavreux C, Suissa S, Saddier P, Bourdès V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. New Engl J Med 2001; **344**: 319–326.

7. Neas LM, Schwartz J, Dockery D. A case-cross over analysis of air pollution and mortality in Philadelphia. Environ Health Perspect 1999; **107**: 629–631.

8. Levy D, Sheppard L, Checkoway H, et al. A case-crossover analysis of particulate matter air pollution and out-hospital primary care arrest. Epidemiol 2001; **12**: 193–199.

9. Sunyer J, Schwartz J, Tobias A, Macfarlane D, Garcia J, Anto JM. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case cross-over analysis. Am J Epidemiol 2000; **151**: 50–56.

10. Redelmeier DA, Tibshirani RJ. Association between cellular telephone calls and motor vehicle collisions. N Engl J Med 1997; **336**: 453–458.

11. Hallqvist J, Moëller J, Ahlbom A, Diderichsen F, Reuterwall C, de Faire U. Does heavy Physical exertion trigger myocardial infection. Am J Epidemiol 2000; **151**: 459–467.

12. Kenneth E. Dixon. A comparison of case-crossover and case-control study designs in a study of risk factors for hemorragic fever with renal syndrome. Epidemiology 1997; **8**: 243–246.

13. Redelmeier DA, Tibshirani R. Interpretation and bias in case-crossover studies. J Clin Epidemiol 1997; **50**: 1281–1287.

14. Hedberg CW, Angulo FJ, White KE, et al. Outbreaks of salmonellosis associated with eating uncooked tomatoes: implication for public health. Epidemiol Infect 1999; **122**: 385–393.