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Study Design

Case-case methods for studying enteric diseases: A review and approach for standardization

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Abstract

Introduction

Studies of foodborne diseases, both to identify the causes of sporadic illnesses and investigation of outbreaks, typically utilize case-control study designs. However, this methodology requires intensive time and resources and is prone to selection and recall biases. Case-case studies have recently been utilized as alternatives. These study designs can be conducted in less time, with far fewer resources and, given the highly selective nature of foodborne case reporting, both selection and recall bias are reduced. Considerable variation remains, however, on how these studies are implemented and how effect measures are interpreted. The aim of this paper is to provide a set of criteria to systematically and consistently choose comparison cases for use in these case-case studies.

Materials and methods

Recent case-case and case-control study designs for foodborne diseases were systematically identified and reviewed on criteria for selection of cases and comparison groups, interpretation of effect measures, source of bias, and resource utilization. Use of this study design for different study goals, outbreak investigation or sporadic disease transmission, were evaluated.

Results

Standardized procedures for selection of comparison cases, common terminology, and effect measures are proposed for case-case study designs, based on whether the study aim is to investigate a foodborne disease outbreak or to study trends in routine transmission. Examples of valid interpretations of resulting odds ratios from the different designs are provided.

Conclusion

Standardization of study design terminology and interpretation, based on the case type, will assist public health agencies and researchers in the effective and appropriate use of this design. The recommendations will allow more comparable results and, potentially, more efficient and timely identification of the cause of a foodborne outbreak.

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Introduction

In 2013 the Robert Wood Johnson Foundation published the report Outbreaks: Protecting Americans from Infectious Diseases[1]. The report found that more than half of the states scored 5 or lower, out of possible 10, on key factors that would protect the nation's health from infectious disease outbreaks. One indicator of reduced readiness was level of funding; over 90% of states had received cuts in public health funding for staff and services in the last fiscal year. Lack of resources limits the ability of health departments and applied researchers to determine the source of an outbreak or determine how risk factors of exposure may be changing over time within their community. These studies require intensive resources to execute, largely through staff time to recruit and interview study subjects.

For investigation of foodborne outbreaks, the most utilized study design is the case-control study. Case-control studies are useful in investigations of pathogens where exposure shortly precedes disease, cases are relatively rare, and results are needed promptly. However, limitations to the case-control study include selection bias, recall bias, and the intensive resources needed to recruit and interview non-ill controls[2].

Furthermore, as it becomes increasingly difficult to recruit appropriate population-based controls, these economic costs and potential biases can increase.

Limited departmental resources have necessitated the development of other study designs to facilitate comprehensive, yet more efficient and cost-effective, investigation of both outbreaks and sporadic transmission of foodborne diseases. Case-case studies are an alternate design in which comparisons of exposures can be made between the cases of interest and another case-population to identify source of outbreaks or risk factors.

The case-case design was first described as a way to analyse case series data, using heterogeneous characteristics among the cases to reveal potential risk factors[3]. The design has also been used to determine risk factors by cancer tumour type[4,5]. It was noted that when comparison cases are drawn from the same source as the cases, selection bias, recall bias and resources required can be minimized.

In 1999, McCarthy and Giesecke theorized the method could be used to study common infectious diseases[6]. Since that time, several published case-case studies of foodborne pathogens produced results comparable to simultaneously administered case-control studies[7,8,9,10,11].

While all case-case studies follow the same basic design, a standard approach for comparison case selection, terminology, and interpretation of results has not been proposed. This paper will (I) review the strengths and limitations of case-case and case-control methods for enteric diseases, (II) discuss the appropriate interpretation of the measure of

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association, (III) assess the more common comparison cases and (IV) recommend a standard strategy for determining appropriate comparison cases, based on the goals and aims of the study.

Materials and methods

Published studies of case-case investigations of food borne investigations were identified utilizing PubMed, Web of Science and Google Scholar. Search terms included 'case-case enterics', 'case-case foodborne' 'case-case design', 'case-case (various enteric names such as Salmonella, Campylobacter, etc.)', 'case2', and 'case-case-control'. These reviews were limited to journal articles published in English and were conducted from August 2011 to December 2012.

The resulting published reports were then reviewed by the principal author for methodological advantages and limitations. Comparisons were made in terms of the following key factors: study question, source of cases, source of comparison group (cases or controls), response rate, effect measure and its interpretation.

These factors were then evaluated for system requirements, recall bias, participation/selection bias, representativeness, timeliness, ability to ascertain new or changing risk factors and cost. Potential comparison cases were categorized as (I) same disease, different characteristics (II) same disease, different time period or (III) different disease, similar symptoms or reporting process.

Based on this systematic review, standardized methods for both risk factor identification and outbreak investigation for the selection of appropriate comparison cases are proposed.

Also, since the review suggested a wide variety of interpretation of the odds ratio for a case-case study design, recommendations were included on how to report and interpret the odds ratios.

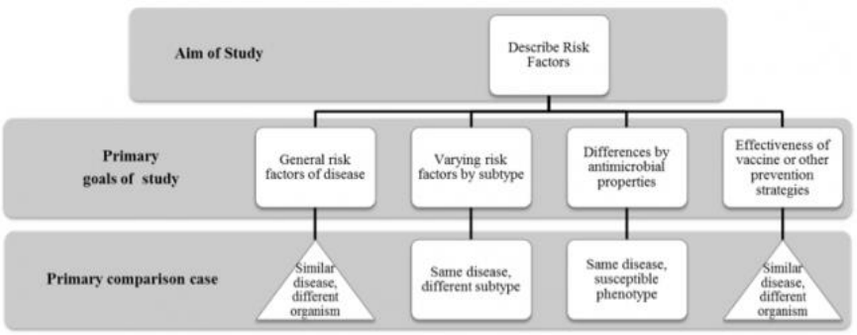

Figure 1: Comparison Case Selection for Studies Aimed at Describing Routine Risk Factors of Disease.

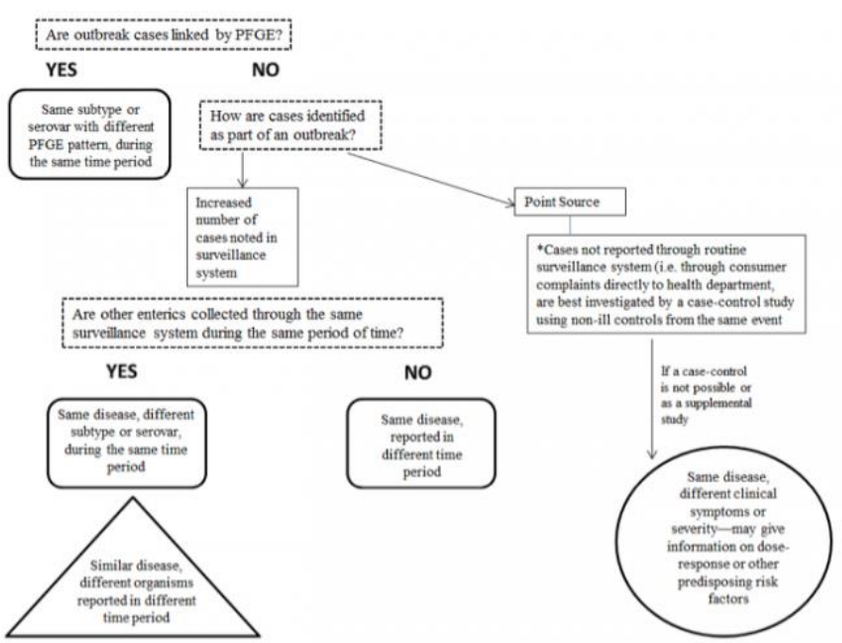

Figure 2: Comparison Case Selection for Studies Aimed at Determining the Source of a Confirmed or Suspect Outbreak.

Results

The list of 17 case-case studies of enteric infections published as of December 31, 2013 is presented in table 1 by goal of the study: outbreak investigation or identification of risk factors. Studies were selected that represented a wide variety of enteric agents (e.g. viruses, bacteria, and parasites) both those that are most commonly associated with outbreaks (e.g. Salmonella and Norovirus) and those that are commonly reported at high levels but routine or sporadic enteric disease (e.g. Campylobacter). These studies show the variety of ways in which this study design can be used, along with the study questions and results that can be obtained using this method.

Overview of strengths and limitations of case-case studies compared to case-control studies

Identification and recruitment of non-ill controls in case-control studies can be time consuming and challenging[12]. This process can add days or even weeks to an outbreak investigation, during which time additional people may be exposed and become ill. Case-case studies, using existing data from comparison cases, have the potential to facilitate timely analyses making this one of the greatest design advantages.

It is generally agreed that a case-case study can reduce both selection and recall bias compared to a corresponding case-control study[6,10,13,14]. Table 2 summarizes strengths and

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weaknesses associated with recall bias, misclassification bias, representativeness, and identification of novel risk factors between case-case studies and case-control studies. The following section highlights issues with selection bias and resource utilization for enteric infections.

Selection Bias

The greatest limitation of case-control methods specific to enteric diseases is selection bias which can arise from two separate sources; (1) selection of non-ill/population-based controls as a comparison group and (2) selection of cases reported through a routine surveillance system. The first is a widely accepted limitation of all case-control studies[2] but will be considered here in the context of enteric disease studies with population-based recruitment.

Reported cases vs. non-ill/population-based controls: Reported cases are a highly selective group. For moderate foodborne illnesses, it is estimated that reported cases only represent 2.5% or less of the population - people who, if they became ill would complete the process to become a reported case[4].

Thus, if a study has a non-ill control group that is representative of the general population, it is unlikely to represent the population from which the cases arose. Therefore, differences that lead a case to be reported (e.g. socioeconomic status, access to care, chronic conditions, etc.) may also create a selection bias between cases and non-ill controls[6]. A case-case study using comparison cases selected in the same manner reduces this bias.

Reported cases vs. non-reported cases: A second source of bias is unique to diseases with low efficiency surveillance systems. As an example, in the United States only about 1 in 30 cases of Campylobacter and Salmonella are reported to a health department [15]. One assumption of a case-control study is that recruited cases are representative of all cases, but clearly cases of reported enteric disease are not a random selection of all cases.

They must go through a series of steps to be included in a surveillance system; become ill, seek medical care, have a stool specimen taken, have the specimen tested appropriately in the lab and finally be reported by a laboratory to the surveillance system. This process can lead to differential reporting due to severity of disease, age, socioeconomic status (SES), chronic health conditions, medications, ethnicity or access to care.

These differences are also likely to differentially affect the exposure history, not simply the outcome, of reported versus non-reported cases[6].

Resources

In the absence of a clear point source outbreak, case-control studies are expensive and time consuming for health departments to conduct every time an elevated number of cases are detected. However, using the risk factor data being routinely collected by most health departments for reported foodborne disease cases, a case-case analysis can be efficiently run to determine factors associated with the observed number of cases become elevated. For a public health response, this reduction in time, cost, and effort are the most important strengths of a case-case study. In 2009, the U.S. Council to Improve Foodborne Outbreak Response (CIFOR) published recommend-ations[16] and a toolkit[17] that suggested conducting case-case investigations to aid in outbreak investigations, however provided little guidance on implementation or interpretation of results.

Interpretation of the Resulting Odds Ratio

Like case-control studies, case-case studies can utilize the odds ratio as its measure of association. Odds ratios (OR) are calculated through simple 2x2 tables or through logistic regression modelling. The OR for the case-case study design must be interpreted carefully as the meaning is different from traditional case-control studies. Because the comparison group was also ill, the case-case OR should be interpreted as a magnitude of association that describes the direction of the relationship between the risk factor and the cases of interest compared to the comparison cases. Furthermore, the interpretation can vary based on the type of comparison case selected. The three potential interpretations are:

(1) OR>1 for risk factor A: In a case-control study, the conclusion of a significant odds ratio over 1.0 would be that risk factor A is associated with the presence of disease. For a case-case study where the comparison cases are due to the same organism, risk factor

A is in excess of its typical occurrence in a case population. For example, raw dairy consumption is a common risk factor among Campylobacter cases compared to non-ill controls[18,19,20]. A comparison of Campylobacter cases to each other with an observed OR>1.0 for raw dairy would indicate that the cases (for example, outbreak cases) had an even higher rate of exposure than the comparison cases (for example, routine cases) and hence, also any non-ill controls.

If a comparison-case population is selected that does not generally report the specific risk factor, the interpretation is similar to a case-control study. For example, while raw dairy is a risk factor for many enteric pathogens, it is not a known risk factor for either cases of Giardia[21] or Cryptosporidium[,22,23] which are more commonly associated with untreated water[24]. The pattern of raw milk consumption is likely to be similar between these comparison cases and non-ill controls.

(2) OR=1 for risk factor B: A null result in a case-case study indicates that there is no heterogeneity between the cases of interest and the comparison cases for exposure to risk factor B. This does not mean that risk factor B is not associated with the cases of interest; it only indicates that the magnitude of the association is similar for both sets of cases.

If, for example, the cases of interest and comparison cases are Giardia and Cryptosporidium, exposure to

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Table 1: Published Case-Case Studies of Enteric Infections.

Author & Study Year	Cases of Interest	Comparison Cases	Study Question	Type of Comparison Case	Results
STUDIES USED TO SOLVE OUTBREAKS					
Krumkamp[10] 2003 C-C	outbreak strain of Salmonella	all other reported Salmonella spp. in same time & space	Can surveillance data be used to help solve an outbreak of Salmonella?	same disease, different subtype	Case-case: high ORs for beef & pork ; Case-control: links to specific butcher shop
Gobin[7] 2010 C-C (-)	non-travel S. enterica Java	non-travel related S. Enteritidis	Is dining out a risk factor? What restaurant foods are highest risk factors?	same disease, different subtype	Salad vegetables implicated but no confirmation
Gaulin[26] 2009	PFGE matched O157:H7	O157:H7 w/ diff PFGE - same time period	Can case-case be used to solve outbreak & match exact probability results?	same disease, different PFGE	Raw cheese
Giraudon[27] 2005	severe outbreak cases	non-severe outbreak cases	Is there a difference in risk factors by severity of disease?	same disease, different clinical symptoms	Certain foods associated with more severe illness
deValk[28] * 1999-2000	2 outbreak strains of Listeria	sporadic cases of Listeria dx during same time	What is causing the outbreak?	same disease, different PFGE	Jellied pork tongue
CDC-MMWR[29]* 1998	Outbreak strain of Listeria	sporadic cases of Listeria dx during same time	What is causing the outbreak?	same disease, different PFGE	Hotdogs
Harker[30] 2008 C-C (-)	S.typi- specific phage	S. enteritidis	What is causing the outbreak?	same disease, different subtype	Reptile feeder mice
STUDIES USED TO DESCRIBE ROUTINE RISK FACTORS					
Aiken[14] 2004-2007	non-Enteritidis Salmonella	Campylobacter	What is the risk of Salmonella due to reptiles?	similar disease, different organism	Much higher risk seen for Salmonella compared to Campylobacter especially for younger ages
Gillespie[31] 2001	C. coli	C. jejuni	Can case-case be used to generate hypotheses of risk factors?	same disease, different subtype	Different risk factors by subtype
Sopwith[32] 2003-2006	C. coli	C. jejuni	What are the risk factors for C. coli?	same disease, different subtype	Some different risk factors by subtype
Wilson[13] 2006	All major enterics	All Campylobacter cases	National level data - can case-case be used to study trends in enteric diseases?	similar disease, different organism	Differences observed that match well known risk factors
Wingstrand[11] 2000-2001 C-C	Campylobacter	non-Campylobacter GI cases	Case-case vs. case-controls	similar disease, different organism	Same results for most with exception of travel & raw water
Gillespie[33] 2000-2001	C. jejuni cases-reporting others ill	C. jejunicases - not reporting others ill	Are point source outbreaks of Campylobacter more common that thought? Use reports of 'others ill'	same disease, different risk factor	Different risk factors for those reporting knowing others ill that not knowing others ill
Bellido-Blasco[34] 2009	Rotovirus cases	Cases of similar disease, not rotovirus	What is the rotovirus vaccination effectiveness?	similar disease, different organism	Rotovirus vaccine effective
Kist[9] 1988-1992 C-C	S. Enteritidis	other Salmonella serovars	What are the risk factors for S. Enteritidis & cause of increase?	same disease, different subtype	Raw eggs likely source of infection
CSSSC[35]** 2000-2001	Ciprofloxicin resisitant C. jejuni	Ciprofloxicin susceptible C. jejuni	What risk factors are associated with resistance to ciprofloxicin in Campylobacter jejuni?	same disease, different anti-microbial property	Foreign travel associated with increased risk of ciprofloxicin resistance
Kassenborg[8] 1998-1999 C-C	Fluoro-quinolone-resistant C. jejuni	Fluoroquinolone-susceptible C. jejuni	What risk factors are associated with resistance to fluroquinolone in C. jejuni infections?	same disease, different anti-microbial property	Foreign travel associated with increased risk of fluroquinolone resistance

* Referred to as case-control study but all controls were other cases. ***Campylobacter* Sentinel Surveillance Scheme Collaborators
C-C: Concurrent case control conducted; C-C (-): Concurrent case control study attempted but unable to recruit enough controls

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Table 2: Advantages (+) and Limitations (-) of Case-Control and Case-Case Methodologies.

	Case-Control Methodology	Case-Case Methodology
Selection Bias	(-) Population-based controls are identified and recruited through a different process than the cases.[2]	(+) Cases and control-cases both identified through same surveillance system.[6]
Recall Bias	(-) Occurs when controls recall information differently from cases by virtue of not experiencing the disease.	(+) Reduced due to both groups experiencing some symptoms. May be relevant for comparisons of different subtypes or agents that result in more severe symptoms or different incubation periods.
Information Bias	(-) Unknown whether controls are truly disease free. Specifically known as a misclassification bias.	(-) Possible; risk factors for some diagnoses may be well known to interviewer and possibly the case, leading to additional information on these risk factors reported.[13]
Representative	(+) Measures exposure prevalence of population through random selection of non-ill controls.[31] Allows for exposure comparison between people who were ill and those who were not ill.	(-) Selection of controls based on factors related to exposure – may not represent true exposure prevalence of larger population. (-) Different from general risk factors seen when compared to healthy people. Will restrict the range of exposures that can be studied but is predictable for a known disease.[6]
Interpretation of Odds Ratios	(+) Standard measure of association used.	(-) Measures of effect should be interpreted cautiously with regard to what group is being used as the comparison cases.[13]
Identification of New or Unique Risk Factors	(+) Able to determine prevalence of risk factors, otherwise cannot adequately determine magnitude of direction for the population at risk. (+) Longer questionnaires used in case-control studies may allow for identification of rare risk factors.	(-) Risk factors may be underestimated or not identified because present in both groups, but useful to generate hypotheses for other studies. (+) If analysis is run often, it may detect changes in risk factors not otherwise found.[13] (-) Questions about rare risk factors may not be on routine surveillance form for analyses.
System Requirements	(+) Can be performed even with inadequate surveillance system because all participants will be interviewed during study or part of outbreak investigation.	(-) Missing data will restrict analyses. Method more effective with detailed surveillance data.
Recruitment	(-) Difficult to recruit population-based controls.	(+) Cases and comparison cases already in the routine surveillance system (+) Can utilize as many comparison cases as needed based on study's power needs
Cost	(-) $$-$$$	(+) $-$$
Timeliness	(-) In outbreak investigations, additional time is needed to identify, recruit and interview controls interviews leading to an increased time until analyses complete.	(+) Can be done quickly in an outbreak following case interviews utilizing existing comparison case data
Effort	(-) Conducting large studies often require a large number of staff hours for interviews, data management and analysis.	(+) Analysis can be done easily

untreated water and consumption of raw dairy may both yield null results. While raw dairy is not associated with disease, the null result of exposure to untreated water can mask the similar elevated magnitude of the association with disease for both Giardia and Cryptosporidium. Case-case studies that use comparisons from the same organism may be particularly subject to null results due to similar risk factor profiles.

(3) OR <1 for risk factor C: Unlike a case-control study where an odds ratio under 1.0 would indicate that risk factor C was 'protective' against disease, the case-case interpretation is simply a matter of reference and may not be interpreted as a real reduction in risk. Continuing with the example of Giardia and Campylobacter, if Giardia were the cases of interest, consumption of raw dairy will likely result in an OR<1 compared to Campylobacter. This simply indicates that it is either not a risk factor for Giardia or significantly less compared to the association with Campylobacter for which it is a known risk factor.

Categories of potential comparison cases

One of the primary issues with valid conduct of case-case studies is the selection of the comparison cases. Comparison cases typically are one of

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Table 3: Selected Comparisons among Potential Comparison Cases.

	Same Disease, Different Characteristics (PFGE sequence patterns, subtype or antimicrobial properties)	Same Disease, Different Time Period	Different Disease with Similar Symptoms and Reporting Process
Common Uses	- Outbreak investigations - Describe risk factors for routine infections - Identify causes of matching PFGE clusters with smaller number of cases	- Outbreak investigations - Trend analyses of risk factors	- Outbreak investigations - Describe risk factors for routine infections
Advantages	- Same systems for surveillance and reporting. - Same seasonal patterns - Same or very similar questionnaire - Same time period of exposure - Takes advantage of routine and outbreak cases often being linked to different risk factors	- Same systems for surveillance and reporting. - Common seasonality for historical and current cases. - Same or very similar questionnaire - Potentially large data set based on annual number of cases and number of years of available data.	- Same systems for surveillance and reporting. - There may be more cases of the comparison disease available – increases analytical power. - Can match cases on potential confounding factors such as gender, age and location. - Same time period of exposure
Dis-advantages	- For rare disease, limited number of comparison cases reported during the same time period. - Requires laboratory diagnostics on subtype or PFGE pattern; may not be available for all reported cases.	- May be difficult to detect a risk factor that is the same for both historical and current cases.	- Resulting odds ratios given based on a comparison to another disease. - Questionnaire may focus on different risk factor(s) making a direct comparison difficult.
Information Bias	- For cases identified as part of a known cluster, extended questionnaires may be conducted on additional exposures not asked for routine cases.	- Similar symptoms and laboratory testing - If knowledge of the disease has changed, emphasis of certain risk factors may be different from one point in time to another. - Dietary habits could change over time.	- Potential risk factors for a more commonly known disease may be reported more readily. - Possible if different tests are more sensitive and find a greater number of cases of one type over another. - Possible reporting bias due to differences in reporting efficiency.
Recall Bias	- Questionnaires may be longer for suspect outbreak cases than sporadic cases. May increase recall if more specific exposures asked.	- Limited between cases of the same disease with similar incubation periods. - May have different questionnaire for outbreak cases.	- Possible if one disease has a much longer incubation period than the other. Longer time from the exposure to the interview could affect accuracy of the recalled foods.
Selection Bias	- Recruitment for interview may be greater for case tied to a known cluster than routinely reported cases.	- Greatly reduced because it is the same disease being reported by the same surveillance system - Can be randomly selected from same surveillance system if comparing to a matched case-control	- If the comparison disease has more severe symptoms, it may be more likely to be reported and tested for.

PFGE: Pulse Field Gel Electrophoresis – molecular sequence pattern method used by Centers for Disease Control to identify national clusters of foodborne disease due to common exposures.

three categories based on the type of organism, time of onset and set of symptoms. The following section illustrates the importance of selecting appropriate comparison cases by describing three strategies for identifying comparison cases. Table 3 summarizes each of these strategies and associated strengths and limitations. All of these comparison case strategies have been used successfully and may prove useful for a variety of diseases, especially when the recruitment of non-ill controls becomes is particularly challenging.

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Same Disease, Different Characteristics
There are many ways in which an infectious organism can be differentiated. One system is based on different characteristics of the same disease: (1) different subtypes of the same disease (while technically these are different species, they are often not differentiated in the reporting system), (2) different PFGE patterns of the same subtype and (3) different antimicrobial susceptibilities.

Same Disease, Different Time Period
Another way cases of the same disease can be used as comparison cases is to compare historical cases to current cases. This idea was proposed by Wilson, et. al.[13] as a way of tracking how risk factors may change over time. Like other comparison cases that are the same disease as the cases of interest, historical surveillance case data have the advantages of the same reporting, symptomology, seasonality and questionnaire design (with some exceptions to questions that may be added or changed over time). While risk factors that remain the same will not be detected, these comparison cases can be used to track changes in attributable risk over time and may play an important role in outbreak investigations.

Different Disease, Similar Symptoms and Reporting Process
A third way in which comparison cases can be selected is to choose a disease that is similar in its clinical symptomology and is reported through the same surveillance system as the cases of interest. This method has been used to help describe the routine risk factors of various infections by comparing one enteric infection to other enterics, either by specific organism[13] or even comparing, for example, Campylobacter to all non-Campylobacter cases reported through the same system, during the same time period[11,13]. The limitation of this method is that the investigators must know the common risk factors for the reference disease used. If there are any common risk factors among the diseases, a null association as described above will occur.

Discussion

The case-case methodology for enteric diseases is a promising study design for use in enterics research and investigation, however, is not limited to this field. Case-case studies can be a cost-effective means for health departments and researchers to use existing data to investigate outbreaks and identify risk factors of disease. However, there needs to be appropriate selection of comparison of cases based on study aim, appropriate interpretation of the measures of effect, and standardized, high quality surveillance data are necessary to make the best use of case-case analysis.

Selection of comparison cases based on study aims and goals
As an aid to compare results across studies and improve understanding of disease risk factors, we propose a systematic strategy for selection of comparison cases based on the primary aim of the study. Figure 1 outlines a strategy for use in selection of comparison groups for sporadic case investigations and figure 2 outlines the strategy for outbreak investigations. Comparison cases for outbreaks should be selected based on availability of case data and how the outbreak is detected.

As with traditional control groups, the best choice of a comparison case group will be those individuals that are similar to the cases of interest with the exception of the risk factors that lead to the disease in question. The ultimate goal of comparison case selection is to reduce bias and the resources needed to conduct the study.

Standardization of terminology and standardized questionnaires
Terminology used for comparison cases is highly variable. Earlier studies more often use the term 'control' or 'control-case' to describe the comparison cases. While this terminology implies the role these cases are playing in the analyses, it can lead to confusion as to what constitutes a control. Recent publications refer to them as the 'comparison cases' or explicitly indicating the specific organism or serotype they represent. We suggest future case-case studies reference the comparison cases by name to help distinguish case-case results from case-control results and restrict use of the term 'control'.

While questionnaires for different diseases must address different risk factor profiles, questions about common risk factors should be the same to facilitate case-case comparisons. For comparison of findings with other agencies, any potential standardization and establishing benchmarks of surveillance systems are critical[25]. This can be facilitated by national or state level agencies or organizations.

Research Needs
One area that warrants further study is the evaluation of the cost-benefits of case-case versus case-control studies. These studies should include economic benefits such as reduced staff time, as well as potential public health benefits such as a more timely identification of a contaminated food source.

Additional analyses to determine the comparability of results between concurrently conducted case-case and case-control studies are also necessary to determine in what specific situations each method is of most use.

Conclusion

Case-case studies will not replace case-control studies, but under certain circumstances they can be used to answer questions efficiently with minimal bias. Unlike many other diseases, foodborne diseases have the advantage of regular data collection occurring through routine surveillance systems at state and local health departments. These case data are often under-utilized and, at a minimum, can be used to generate hypotheses about the risk factors that are leading to disease within a community. Utilization of this study design allows public health agencies and researchers to investigate

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sources of disease in the face of shrinking resources. The use of the standardized approaches outlined here will help to make the results from both academic and applied fields complement each other.

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