



Third Edition

Foodborne Infections and Intoxications

Edited by
Hans P. Riemann and Dean O. Cliver

Food Science and Technology, International Series



FOODBORNE INFECTIONS AND INTOXICATIONS

Food Science and Technology International Series

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Foodborne Infections and Intoxications

Third Edition

Edited by

Hans P. Riemann and Dean O. Cliver

School of Veterinary Medicine
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Contents

Contributors	x
Preface to the third edition	xiii
Preface to the second edition	xv
Preface to the first edition	xvi
Dedication	xvii
PART I Incidence of Foodborne Disease	1
1 Epidemiology of foodborne diseases	3
<i>Philip H. Kass and Hans P. Riemann</i>	
1. Introduction	3
2. Historical aspects	5
3. Contemporary problems	5
4. Epidemiological investigations of foodborne diseases	10
Bibliography	24
2 Microbial food safety risk assessment	27
<i>Anna M. Lammerding and Ewen C. D. Todd</i>	
1. Introduction	27
2. Movement away from traditional methods to evaluate the safety of food	29
3. Managing risk through risk assessment	30
4. Risk assessment for microbial hazards	34
5. Conducting a risk assessment	35
6. Applications of microbial risk assessment techniques for food safety ..	45
7. Summary	47
Bibliography	49
PART II Foodborne Infections	55
3 Salmonella infections	57
<i>Kåre Mølbak, John E. Olsen, and Henrik C. Wegener</i>	
1. Historical aspects and contemporary problems	57
2. Characteristics of <i>Salmonella</i>	67

	3. Nature of the infection in man and animals	78
	4. Prevalence of <i>Salmonella</i> in foods and feeds – principles for control ...	88
	5. Foods most often associated with human infections	103
	6. Epidemiology of salmonellosis	103
	7. Principles of detection of <i>Salmonella</i>	109
	Bibliography	115
4	<i>Clostridium perfringens</i> gastroenteritis	137
	<i>R. G. Labbe and V. K. Juneja</i>	
	1. Historical aspects and contemporary problems	137
	2. Characteristics of the organism	138
	3. Nature of the disease	148
	4. Epidemiology	152
	5. <i>C. perfringens</i> enterotoxin	156
	6. Detection of the organism and enterotoxin	157
	Bibliography	164
5	<i>Vibrio</i> infections	185
	<i>Riichi Sakazaki, Charles Kaysner, and Carlos Abeyta, Jr</i>	
	1. <i>Vibrio parahaemolyticus</i>	185
	2. <i>Vibrio vulnificus</i>	191
	3. <i>Vibrio cholerae</i>	193
	Bibliography	198
6	<i>Escherichia coli</i>	205
	<i>Pina M. Fratamico and James L. Smith</i>	
	1. Introduction	205
	2. Characteristics of <i>Escherichia coli</i>	207
	3. Enteroinvasive <i>Escherichia coli</i> (EIEC)	208
	4. Diffusely adherent <i>Escherichia coli</i> (DAEC)	210
	5. Enteroaggregative <i>Escherichia coli</i> (ESEC)	210
	6. Enterotoxigenic <i>Escherichia coli</i> (ETEC)	214
	7. Enteropathogenic <i>Escherichia coli</i> (EPEC)	222
	8. Enterohemorrhagic <i>Escherichia coli</i> (EHEC)	224
	Bibliography	239
7	<i>Campylobacter jejuni</i> and related pathogens	259
	<i>Sean F. Altekruise and Guillermo I. Perez-Perez</i>	
	1. <i>Campylobacter jejuni</i>	259
	2. Related organisms	270
	3. Summary	276
	Bibliography	276
8	<i>Yersinia</i> infections	289
	<i>Truls Nesbakken</i>	
	1. Historical aspects and contemporary problems	289
	2. Classification	290
	3. Differentiation of <i>Y. enterocolitica</i> from other <i>Yersinia</i> species	290

4. Virulence factors	292
5. Ability to survive and grow	292
6. Nature of the infection in man	293
7. Nature of infection or carrier state in animals	294
8. Foods most often associated with sporadic cases and outbreaks ...	296
9. Sporadic cases	297
10. Outbreaks	299
11. Principles of detection	300
Bibliography	302
9 Listeria monocytogenes infections	313
<i>Franco Pagotto, Nathalie Corneau, and Jeff Farber</i>	
1. Historical aspects and contemporary problems	313
2. Characteristics of <i>Listeria</i>	314
3. Nature of Infection in man and animals	320
4. Prevalence of <i>Listeria</i> in foods, feeds and water	320
5. Foods most often associated with human infections	327
6. Principles of detection of <i>Listeria</i>	328
7. Treatment and prevention of listeriosis	330
Bibliography	331
10 Infections with other bacteria	341
<i>Maha N. Hajmeer and Daniel Y. C. Fung</i>	
1. Introduction	341
2. Synopses of individual bacteria	342
3. Conclusion	362
Bibliography	363
11 Infections with viruses and prions	367
<i>Dean O. Cliver, Suzanne M. Matsui, and Michael Casteel</i>	
1. Historical aspects and contemporary problems	367
2. Hepatitis A Virus (HAV)	369
3. Hepatitis E Virus (HEV)	379
4. Noroviruses	385
5. Rotaviruses	393
6. Enteroviruses	398
7. Other viruses	402
8. Surrogates	405
9. Prions	409
10. Overview	415
Bibliography	416
12 Foodborne parasites	449
<i>J. P. Dubey, K. D. Murrell, and J. H. Cross</i>	
1. Introduction	449
2. Meatborne protozoa and helminths	449
3. Fishborne helminths	469

	4. Protozoa and helminths disseminated in fecally contaminated food and water	473
	Bibliography	476
PART III	Foodborne Intoxications	483
13	<i>Clostridium botulinum</i>	485
	<i>Nina G. Parkinson and Keith A. Ito</i>	
	1. Introduction	485
	2. Historical aspects and contemporary problems	486
	3. Characteristics of <i>Clostridium botulinum</i>	487
	4. Characteristics of the toxin	493
	5. Nature of the intoxication in man and animals	493
	6. Therapeutic use of the toxin	498
	7. Other potential uses of the toxin	498
	8. Animal botulism	499
	9. Distribution of spores in food and the environment	501
	10. Foods associated with botulism	503
	11. Detection of <i>Clostridium botulinum</i>	504
	12. Detection of botulinum toxin	506
	Bibliography	508
14	Staphylococcal intoxications	523
	<i>Merlin S. Bergdoll and Amy C. Lee Wong</i>	
	1. Historical aspects and contemporary problems	523
	2. Characteristics of <i>Staphylococcus aureus</i>	526
	3. The toxins	529
	4. Nature of the intoxication in man and animals	540
	5. Prevalence of <i>S. aureus</i> in foods	543
	6. Foods most often associated with staphylococcal food poisoning ..	543
	7. Principles of detection of <i>S. aureus</i>	544
	8. Principles of detection of the enterotoxins	545
	9. Summary	551
	Bibliography	552
15	<i>Bacillus cereus</i> gastroenteritis	563
	<i>Heidi Schraft and Mansel W. Griffiths</i>	
	1. Introduction	563
	2. Historical aspects and contemporary problems	563
	3. Characteristics of <i>Bacillus cereus</i>	564
	4. Characteristics of <i>Bacillus cereus</i> food poisoning	565
	5. Presence, growth and survival of <i>B. cereus</i> in foods	571
	6. Isolation and identification	573
	7. Outbreaks caused by <i>Bacillus</i> spp. other than <i>B. cereus</i>	576
	8. Treatment and prevention	577
	Bibliography	577

16	Mycotoxins and alimentary mycotoxicoses	583
	<i>Fun S. Chu</i>	
	1. Introduction	583
	2. Mycotoxins produced by toxigenic fungi	584
	3. Natural occurrence and toxic effects of selected mycotoxins	585
	4. Intoxication from naturally occurring toxic fungal metabolites	600
	5. Modes of action of mycotoxins	607
	6. Preventive measures	621
	7. Concluding remarks	626
	8. Abbreviations	627
	Bibliography	629
17	Miscellaneous natural intoxicants	663
	<i>Eric A. Johnson and Edward J. Schantz</i>	
	1. Introduction	663
	2. Bacterial toxins	669
	3. Seafood toxins	673
	4. Plant toxins	690
	5. Other foodborne toxicants	699
	6. Laboratory practices, conclusions and perspectives	700
	Bibliography	701
PART IV	Prevention of Foodborne Disease	711
18	Effects of food processing on disease agents	713
	<i>Roberto A. Buffo and Richard A. Holley</i>	
	1. Introduction	713
	2. High-temperature preservation	714
	3. Low-temperature preservation	721
	4. Multiple intervention technology	724
	5. Fermentation and safety	731
	6. Food packaging	739
	7. Control of microorganisms by chemical antimicrobials	746
	8. Control of microorganisms by natural antimicrobials	754
	9. Alternative innovative technologies	772
	10. Plant hygiene and contamination during food processing	791
	11. Predictive microbiology	799
	Bibliography	802
19	Food safety	833
	<i>Ivone Delazari, Hans P. Riemann, and Maha N. Hajmeer</i>	
	1. Overview	833
	2. Preharvest food safety	833
	3. Postharvest food safety	842
	4. Comments and conclusions	876
	Bibliography	877
	Index	885

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Preface to the third edition

A quarter of a century has passed since the second edition of *Foodborne Infections and Intoxications* was published. Significant discoveries and developments have taken place during this time, and many journal articles and several books dealing with foodborne pathogens have been published. Some important foodborne pathogens (e.g. noroviruses, enterohemorrhagic *Escherichia coli*) were unknown at the time of the second edition, and organisms such as *Yersinia* and *Campylobacter* were not conclusively proven to be foodborne.

In this third edition of *Foodborne Infections and Intoxications*, experts present updated accounts of the known characteristics of the most important foodborne pathogens, including their host ranges and the characteristics of the diseases they cause. The present volume also has a completely revised chapter on the epidemiology of foodborne diseases, with emphasis on investigation procedures, and a new chapter on risk assessment has been added. The chapter on the effects of food-processing procedures has been expanded to include a number of newer techniques, and the chapter on food safety presents a detailed discussion of hazard analysis-critical control points (HACCP) as a tool to assure safety. Four new chapters have been added, on *E. coli*, *Campylobacter* and related organisms, *Yersinia*, and *Listeria*, in addition to a chapter on other natural toxins (not including mycotoxins).

Much new information about the detection and identification of foodborne pathogens has been presented in books and articles in recent years. Still, about half the reported foodborne disease outbreaks in countries like the US have no identified agent. Without doubt many of these outbreaks are caused by viruses, which suggests a need for virus-detection procedures that can be applied by laboratories routinely charged with testing of suspect food samples. Since sampling and testing *per se* do not prevent foodborne disease outbreaks, there is also a need for research to develop effective interventions against common foodborne diseases and methods to assure the implementation of such interventions; the last two chapters of the book address this need.

There is, furthermore, a need for better setting of research priorities on foodborne diseases; some diseases, like human prion diseases, are so rare that even a 90 per cent

reduction in incidence would have negligible public health significance. The chapter on risk assessment describes an important tool for setting priorities.

The editors especially thank the authors for contributing their vast expertise to this book.

Hans Riemann
Dean Cliver

Preface to the second edition

The organization and content of this edition follow the pattern of the first edition, but some changes have been made. The addition of a chapter on epidemiology provides information on the principles of foodborne disease transmission, the magnitude of the foodborne disease problem, and investigation of foodborne disease outbreaks. The chapters on laboratory methods and poisonous plants and animals have been deleted because these topics are adequately covered in other recent texts. A more extensive and detailed discussion of the foodborne infections and intoxications and their control has been provided. We hope that the changes will make the volume more useful as a reference work and textbook.

We are indebted to our co-authors for their willingness to make contributions. Special thanks are due to Ms Mary Jeanne Fanelli for excellent editorial assistance and to the staff of Academic Press for their cooperation.

*Hans Riemann
Frank L. Bryan*

Preface to the first edition

The broadness of the subject of this volume has made selectivity a necessity. Several types of food poisoning have not been included, such as those caused by toxic chemicals intentionally or unintentionally added by man. Among the naturally occurring agents only those considered most important have been included.

The content of this work could have been organized in several ways. We have chosen to group together those agents which must be present in food in a viable state in order to cause disease, although the disease which is provoked is often termed food poisoning (e.g. Salmonella food poisoning, perfringens food poisoning). The subdivision of the chapter on botulism into one on type E and another on types A, B, and F was motivated by the higher incidence of type E botulism in recent years and the accumulating literature dealing specifically with type E.

The purpose of the chapters on laboratory methods and food processing and preservation is to make the treatise more useful to readers who have special interests in these aspects of foodborne infections and intoxications. Since these chapters deal with a variety of organisms which are discussed in other chapters some repetition and scatter of information have resulted.

I am indebted to my co-authors for their willingness to make contributions without which this work could not have materialized. I also gratefully acknowledge their advice, understanding, and patience. I am indebted to Dr G. M. Dack for his encouragement and advice in connection with the planning of this volume. Special thanks are due to Mrs Patricia Akrabawi for excellent editorial assistance and to the staff of Academic Press for their cooperation.

*Hans Riemann
January 1969*

Dedication

While doing the food safety work that has occupied most of our combined 155 years of life, we have had the good fortune to deal with many exceptional scientists, some of whom are no longer with us.

We dedicate this book to the departed who have contributed to it, or would have, including Merlin S. Bergdoll, David A. A. Mossel, Riichi Sakazaki and Edward J. Schantz. Doctors Bergdoll, Sakazaki and Schantz were co-authors of chapters 14, 5, and 17, respectively. Dr Mossel was to have written the foreword to this book as did the late Zdeňek Matyáš to our recent *Foodborne Diseases*, second edition. The contributions of these five scientists to food safety worldwide have been huge. We are grateful to them, and to our younger colleagues who have completed these and other chapters, and have accepted the responsibility to continue this work.

We thank and salute them, one and all.

The editors

Incidence of Foodborne Disease

PART
I

Epidemiology of foodborne diseases

Philip H. Kass and Hans P. Riemann

1. Introduction	3
2. Historical aspects	5
3. Contemporary problems	5
4. Epidemiological investigations of foodborne diseases	10
Bibliography	24

1 Introduction

Chemical, physical and biological agents transmitted by foods cause more than 200 recognized diseases in people (Bryan, 1982). Of these, infectious biological agents are the most important, causing the majority of foodborne disease. To put this figure in perspective, there are presently 412 known human infectious diseases, 118 of which are primarily found in humans but may also be found in animals, and 62 of which are principally animal infections but are also present in people. Among those diseases shared by humans and animals, 35 are widespread among animals, of which 12 are shared with livestock; 7 with non-human primates; several others with birds, fish or insects; and 2 with plankton (Morse, 1995). Only some of these infections are known to be foodborne, and the most important among these are the subjects of chapters in this book. It would be a grievous error, however, to believe that we have seen the entirety of infectious agents that are transmissible to people through food. So-called 'new' or 'emerging' foodborne agents have been discovered continuously over the years, from variants of well-known infectious agents such as *E. coli* to unprecedented infectious and non-reproductive agents (e.g. prion diseases such as Kuru and variant Creutzfeldt-Jakob syndrome). Even today, diseases that have traditionally been held to exist only in the realm of animals are crossing the species boundary to humans through routes that remain to be completely elucidated, such as avian influenza. Remarkably, even today no infectious cause is detected in approximately half of all reported foodborne disease outbreaks, making the discovery of 'new' agents virtually inevitable in the future.

Many of the infectious agents capable of causing foodborne diseases can be transmitted in ways other than via food or water. Agents transmitted by the fecal–oral route can cause infection through direct contact among hosts. Others, like *Coxiella burnetii*, the infectious agent of Q-fever, can be transmitted by the respiratory route, and botulism can be caused by wound infection with *Clostridium botulinum*. Some agents, though capable of causing infection by oral transmission, are seldom foodborne. Those agents that are most frequently foodborne are readily capable of occurring in enormous numbers in feces and hence in foods or water contaminated with feces (or other contaminated organic material); examples of these are *Clostridium perfringens*, *Staphylococcus aureus*, and *Bacillus cereus*.

Foodborne disease agents can be classified in different ways. The most common scheme is taxonomic combined with a classification based on mode of action; we have adopted this convention in grouping in the chapters of this book. Classification according to the source of the agent is largely useful only in situations where there can be only one or at most a few possible specific sources, such as in cassava and fugu poisoning. Another classification is based on clinical signs and symptoms of disease; under this scheme agents that use common themes in pathogenicity are grouped together, such as *Shigella*, *Yersinia*, and enteropathogenic *E. coli*. Alternatively, Bishai and Sears (1993) have distinguished foodborne disease organisms by the predominant clinical syndromes that they cause in the following (non-exhaustive) way:

- Nausea and vomiting (*S. aureus*, *B. cereus*, noroviruses, heavy metals, parasites)
- Non-inflammatory diarrhea (*C. perfringens*, *E. coli*, *Vibrio cholerae*)
- Inflammatory diarrhea (non-typhoidal *Salmonella*, *Shigella*, enteroinvasive *E. coli*, enterohemorrhagic *E. coli*, *Campylobacter*, *V. parahaemolyticus*, *Yersinia*, and other enteroinvasive pathogens)
- Neurological signs and symptoms (*C. botulinum*, ciguatera toxin, scombroid toxin, neurotoxic shellfish poisons, mushroom toxins, monosodium glutamate)
- Systemic and miscellaneous symptoms (*Listeria monocytogenes*, *Trichinella spiralis*, group A streptococci, hepatitis A virus, *Brucella* spp.).

It is clear that quite diverse agents can cause similar clinical signs and symptoms of foodborne diseases. This underscores the importance of laboratory identification of the agent in understanding the etiology, treatment and prevention of disease in individuals and in populations. Unfortunately, even with modern, sophisticated laboratory techniques, identification of the agent has not been accomplished in approximately half of the investigated foodborne disease outbreaks in the US to date. This failure of identification may occur because the agent is truly unknown (Mead *et al.*, 1999), because an inaccurate laboratory procedure has been applied, or because of mishandling of samples.

The focus of this chapter is on the epidemiology of foodborne diseases. Epidemiology has as its objective the study of the distributions of disease and health in populations, and how changes to these distributions are affected by causal determinants. The use of knowledge gained from this scientific discipline to effect changes in these distributions is the ultimate validation of epidemiological findings, as exemplified by the now legendary story of John Snow's removal of the handle of the Broad Street pump during a London cholera epidemic in the nineteenth century – an action

that ultimately led to a dramatic decline in the area's disease morbidity (Snow, 1855). Snow's action demonstrated that fecal contamination of drinking water was a 'cause' of cholera many years before the causative agent, *Vibrio cholerae*, was identified, and indeed before the germ theory that microbial organisms could act as pathogenic agents was universally accepted.

2 Historical aspects

A few foodborne diseases, such as botulism, have been recognized and described since early historical times (Dolman, 1964). There is no doubt that the existence of foodborne diseases was recognized much earlier than the actual identification of pathogenic organisms, when humans learned by observation and/or experimentation which food items to avoid. Such proscriptions against certain foods, such as a ban on the consumption of pork in some religions, may too have been originally founded upon perceptive observations combined with rudimentary testing. In the middle of the 1800s, advances in scientific methods led to the identification of certain foodborne parasites, which formed the genesis of modern meat inspection procedures.

Since the dawn of the microbiological era, a great many microbial foodborne disease agents have been identified. By 1960, *Salmonella*, *Shigella*, *C. botulinum* and *S. aureus* were all well-known causes of foodborne diseases. *C. perfringens* and *B. cereus* were added to the list in the 1960s, followed by Norwalk virus in the 1970s; *Campylobacter*, *Yersinia*, 'new' strains of *E. coli* such as O157:H7, and *Cryptosporidium* were added in the 1980s; and *Cyclospora* in the 1990s.

The incidence of foodborne diseases in earlier times is completely unknown. When the human population was largely rural, most food was produced when and where it could be grown, raised or found. The unreliability and frequent unavailability of adequate supplies of food throughout an entire year necessitated storage of certain food items. This essential need led to development of preservation methods such as drying, salting, smoking, fermentation and, where climatic conditions permitted, refrigeration and freezing. Despite being shown later to have a sound scientific basis, food handlers' theory was sometimes better than their practice, and preserved foods undoubtedly sometimes caused food poisoning – which in turn led to further and safer refinements. There is little doubt that the advent of the use of heat in food preparation, delivered in the form of fire, helped to reduce the presence of pathogens (particularly in foods of animal origin), and hence the occurrence of foodborne illnesses.

3 Contemporary problems

3.1 Causes of foodborne diseases

Food itself does not normally cause disease in the short-term, except when it contains intrinsic toxins or allergenic components, or is consumed in toxic or physically incapacitating quantities. Although foods can admittedly be nutritionally deficient or contain substances known to be predictive of adverse long-term health impacts

(e.g. excessive consumption of saturated fat), these effects fall instead within the realm of dietary-induced disease, and are not the subject of this book.

The ‘web of causation’ (MacMahon and Pugh, 1970) and the ‘sufficient-component model of causation’ (Rothman, 1976) are useful and complementary paradigms in unraveling the constellation of causes of foodborne diseases. The ‘web of causation’ dispelled the naïve but long-held and pervasive belief that the predominant determinant of disease in an individual was the presence of a specific agent. Instead, it diagrammatically illustrated the complex interplay between organism, host and environmental factors that inevitably occur before an individual’s transition from a state of health to a state of disease. The ‘sufficient-component model’ postulates that different factors intrinsic to the host, organism and/or environment interact to cause disease; such factors are called ‘component causes.’ A set of minimally acting component causes – those that are minimally sufficient to initiate the transition of an individual from health to disease – are called ‘sufficient causes’. It is important to note that there may be more than one, and indeed many, minimally sufficient sets of component causes that can lead to disease occurrence in a population, though only one sufficient cause exists for a single diseased individual. If a single disease is of infectious origin, then by definition every unique sufficient cause must include as a component cause the presence or influence of the infectious organism; such component causes that are common to all sufficient causes for a disease are designated ‘necessary causes’.

Although single agents are obviously necessary causes, the mere presence of an agent in food or water may not be a component cause because the number of organisms (the dose) may be too low to cause infection or disease. The presence of other component causes besides the organism is inevitable, as illustrated in a study of *Salmonella* infection in poultry by Kinde *et al.* (1996). In this study, *Salmonella* from insufficiently treated urban sewage contaminated a stream that served as the only source of water for local wildlife. Wild animals subsequently became infected and carried the infection into proximate poultry houses, where they went searching for food. Through fecal and/or mechanical contamination of the environment, the poultry became infected, in turn increasing the risk of subsequent infection of humans through meat or eggs. Each component cause stipulated in the web of causation is the result of several antecedents, and the risk of human salmonellosis in this example could have been mitigated by removal of any single component cause, such as proper treatment of sewage, eliminating wildlife, or preventing access of wildlife to poultry houses. A distinct advantage of envisioning causation in this way is that it is not necessary fully to understand the causal mechanisms in their entirety to take preventive measures; elimination of a single component cause renders the set of component causes no longer sufficient. This approach has analogies to hazard analysis and critical control point methods (HACCP), where prevention is achieved through intervention at the critical control points.

3.2 Emerging foodborne diseases

3.2.1 Background and definitions

Mankind occupies a uniquely high position in the pecking order of nature. The single notable exception to this dominance is that people ostensibly can become the very

victims of microbes and parasites that presumably occupy some of the lowest rungs of the evolutionary ladder. All humans are colonized almost from birth by a host of microbes, some of which are potentially pathogenic yet under normal circumstances do not cause disease. Through evolution, our species has acquired the mechanisms necessary to resist many different agents (Burnett and White, 1972). However, present-day exposures of people to a variety of foodborne pathogens readily occur over what formerly were secure geographical barriers, and at a rate so high that human evolution cannot keep pace. Furthermore, the absence (or near absence) of some agents in certain geographical areas leads to immunologically-naïve populations: resistance that would have otherwise been acquired in childhood is absent, leaving a highly susceptible population. For example, in some geographic regions hepatitis A virus infection is widespread, and children become brief shedders followed by active, lifelong immunity at an early age. In contrast, in other geographic areas hepatitis A infections are almost unknown, leaving a population that is very susceptible to infection from virus-contaminated foods. Demographics of human populations in many developing countries have dramatically shifted in only a few generations; with the gradual onset of urbanization and modernization, a further increase in the number of people with heightened disease susceptibility is to be expected.

Emerging foodborne diseases have been defined (Levine *et al.*, 1994) as diseases having one or more of the following characteristics:

- Clinical signs and symptoms differ from those of any diseases that preceded it
- Previously tolerated and acceptable conditions become intolerable
- A previously marginal population (afflicted with a certain disease) gains public voice
- New infection pathways, intermediate hosts, or reservoirs of pathogens evolve because of environmental or social changes.

Clearly an agent never before identified as foodborne also represents an emerging disease even if it may not be truly new (on an evolutionary scale), if it was accidentally overlooked in the past because its identification was never sought or because of inadequate and insensitive laboratory identification techniques. An emerging foodborne disease can also be attributed to a previously recognized foodborne agent when it appears in a population never before affected.

In industrialized countries, different patterns of foodborne disease outbreaks also appear to be emerging. Outbreaks that at one time were more commonly reported from smaller gatherings or cohorts, such as family picnics and church suppers, are now changing in frequency towards a greater occurrence of more diffuse and widespread outbreaks in larger populations (Tauxe, 1997). The globalization of food trade, large-batch production units, and increased consumption of 'fast' (i.e. ready-to-eat) food means that food that does not receive a terminal heat treatment may contribute to changes in outbreak patterns.

3.2.2 Changes in host susceptibility

Susceptibility to foodborne diseases may be altered for a number of reasons. Susceptibility increases as a result of impairment of the immune system caused by

infection (especially AIDS), neoplasia, immune-mediated disease, immunosuppressive therapy used for cancer treatment or to prevent post-transplant organ rejection, and other medications that can alter the ecology of the gastrointestinal tract (notably antibiotics). Children of few years' age are considered more susceptible, and old age is also associated with a decrease in immune response; in addition, the elderly may have decreased gastric-acid secretion (Morris and Potter, 1997).

A 35-fold increase in the incidence of *Campylobacter* infections and a 280-fold increase in *Listeria* infections have been seen in AIDS patients; 5–10% of non-pregnant AIDS patients have developed *Toxoplasma gondii* encephalitis, and 10–20% of AIDS-associated diarrhea is due to *Cryptosporidium* infection (Morris and Potter, 1997).

While the AIDS epidemic may eventually be brought under control, the proportion of the US population that develops cancer, receives organ transplants or reaches old age will almost certainly continue to increase. In the US, white-male cancer incidence increased by 27% between 1973 and 1994; in white females the increase was 18%. Organ transplantation increased by 54% between 1988 and 1996. The proportion of US population over 74 years of age increased by 115% between 1950 and 1995; and of the 29 000 people in the US who reportedly died from diarrhea between 1979 and 1987, 51% were over 74 years old (Morris and Potter, 1997).

3.2.3 Food handling

Other factors contributing to changes in outbreak patterns may include decreased experience in food handling and preparation, and an increase in the number of meals taken outside the home and sometimes prepared by persons with limited training in and understanding of food safety. Less than 50% of consumers are concerned about food safety. There are also an increasing number of women in the workforce living away from home and a greater number of single heads of households; this tends to limit the commitment to food preparation, and consumers seem to be more interested in convenience and saving time than in proper food handling and preparation (Collins, 1997). Furthermore, many consumers are not familiar with the properties of many of the new convenience foods, and the errors they commit in food preparation may occur because they have not absorbed information about how to handle food and protect themselves; that is, messages to the public about the importance of food safety may not have been delivered effectively (Bruhn, 1997). The situation may be exacerbated by the increasing number of vulnerable people and a shrinking public health infrastructure (Altekruse *et al.*, 1997).

The primary production of food occurs increasingly in large batches; this in itself may not pose an increased risk, but can result in widespread distribution of pathogens if and when they occur, and under conditions conducive to pathogen survival. Increasing imports of foods such as fruits and vegetables, grown and processed under undocumented conditions, may also lead to increased exposure to a myriad of bacteria and parasites (Beuchat and Ryu, 1997).

Industrially processed foods such as canned foods have, since the introduction of safe and calculated heat processes, had a very good safety record. However, different types of processing have been and continue to be implemented to provide even fresher, ready-to-use food in innovative packaging (Zink, 1997). These developments

are driven by consumer appeal and competition; they are based on technical inputs from private and public laboratories, and require that distributors and users follow instructions on labels.

3.3 Incidence of foodborne disease

Information about the incidence of foodborne diseases comes from surveillance data usually collected in outbreaks; very little information is available on the incidence of sporadic cases. Outbreak reporting is admittedly incomplete; there is a considerable but unknown amount of underreporting. Attempts have been made (Bennett *et al.*, 1987; Todd, 1989) to estimate the degree of underreporting of foodborne diseases; reported annual cases in relation to the estimated number of cases ranged from about 13% for botulism to 0.01% for infections with *Vibrio* spp. (not *V. cholerae*). The total number of reported cases with known etiology was close to 11 000, while the total number of estimated cases was about 5 million. With this kind of uncertainty, reported numbers of foodborne disease outbreaks and cases may be more misleading than enlightening. However, published surveillance data do permit some comparisons of the magnitudes of incidences related to agent, year, season and other variables. Data compiled between 1985 and 1989 from 21 countries and presented by Todd (1994) indicate that salmonellosis was the most common foodborne disease in these countries except for Cuba, Denmark, Finland and Japan. *Staphylococcus aureus* intoxications ranked high in Cuba, Israel, Japan, Portugal, and Yugoslavia, while *Clostridium perfringens* infections were common in Denmark, Finland, Israel, and Sweden. The differences among countries probably reflect differences in the types of foods consumed (which can vary over time due to immigration and emigration), and differences in laboratory methods and surveillance systems. Reported foodborne disease outbreaks in the US showed no time trends through the periods 1983–1987 and 1988–1992 (Bean *et al.*, 1997), but there may be some trend in the relative frequency of isolation of different agents; *Clostridium perfringens*, *E. coli*, *Salmonella*, and hepatitis A seemed to be on the increase. The most striking feature of the data is that they show that no agent was discovered in between 54% and 64% of the investigated and reported presumptive foodborne outbreaks.

There are apparent seasonal trends in reported foodborne outbreaks in the US (Bean *et al.*, 1997). Outbreaks caused by bacteria peaked in May to August, while outbreaks caused by chemicals had a broader peak, from April to November. The peak for outbreaks caused by bacteria can probably be explained by better growth conditions during the warmer months; the reason for the peak in chemical outbreaks seems less clear. No seasonal trends were observed for parasitic or viral infections.

The 1988–1992 data for the US (Bean *et al.*, 1997) suggest that restaurants dominated among the places where foods contaminated by bacteria were eaten, with homes in second place. However, foods contaminated with bacteria were, in many instances, consumed at what was reported as ‘other places’. For chemical food poisoning and parasitic infections, homes and restaurants ranked even. The interpretation of this information is uncertain because the number of meals consumed at home and at restaurants is unknown, and restaurant outbreaks may be more likely to be reported because more people are exposed.

The vehicles of transmission of foodborne diseases showed no apparent trends during 1983–1987 and 1988–1992 (Bean *et al.*, 1997). Beef, chicken, fruits and vegetables, ‘other’ fish and ‘other’ salads were all high on the list of vehicles, but the list is difficult to interpret because Chinese food and Mexican food are compared to individual food items such as ham, eggs and cheese. Furthermore, in 32–36% of reported outbreaks multiple vehicles were involved, and in 53–63% of reported outbreaks no vehicle was identified. Finally, the vehicles may not even be the sources of infection, but little information is available.

Data have been collected (Bean *et al.*, 1997) on what is called ‘contributing factors’ to foodborne disease outbreaks, and there is no apparent trend in these in the US for the period 1988–1992. Contributing factors are the same as component causes; with respect to bacterial food poisoning, improper holding temperature, inadequate cooking and poor personal hygiene were the leading causes; for chemical food poisoning, unsafe sources and – surprisingly – improper holding temperature were listed as leading causes; for parasitic infections no single cause was predominant; while for viral diseases the dominating cause was poor personal hygiene.

4 Epidemiological investigations of foodborne diseases

4.1 Foodborne disease surveillance

4.1.1 Passive surveillance

Although extensive data in the US are collected through local, state and national agencies, precise information about the epidemiology of foodborne diseases is scarce because it is difficult and expensive to obtain representative (and retrospective) data. Many countries have surveillance systems where outbreaks are reported, with an outbreak generally interpreted as two or more persons who become ill from the same food. Sporadic (single) cases are not reported except where there are specific mandatory requirements. Whether reporting actually occurs depends on the likelihood that afflicted individuals seek medical help, on the probability that the physician submits a sample to a laboratory, on the ability of the laboratory to detect the agent in question, and on the probability that the needed documentation is completed and submitted to a central agency that analyzes and publishes foodborne disease data. These successive sources of potential error mean that not only is there underreporting of disease incidence, but also the reporting is biased because severe cases or a high number of cases from a common source are more likely to be reported. For these reasons, foodborne disease incidence has been likened to the small part of an iceberg observed above water, with the predominant part acknowledged but unobservable. Laboratory diagnostic procedures have been substantially improved in recent years, but there is room for additional improvement because, as noted earlier, no causative agent is found in approximately 50% of reported foodborne outbreaks.

The surveillance alluded to above is also known as ‘passive surveillance’. A few countries have had passive foodborne disease surveillance systems for more than half a century, and an increasing number of countries are using such systems.

Todd (1994) has presented an extensive review of surveillance systems existing throughout the world.

The objectives of foodborne disease surveillance are the following (Todd, 1994):

- Early warning of an illness (real or potential) that could affect a large number of members of a community
- Notifications by physicians of enteric or other specific diseases, that often are foodborne, to a reference laboratory
- Investigations of reports of foodborne illness and reporting of results on a regular basis
- Use of sentinel and special epidemiological studies to determine a more realistic level of morbidity caused by foodborne diseases (this type of activity is generally considered active surveillance).

Guzewich *et al.* (1997), Bryan *et al.* (1997a, 1997b) and Todd *et al.* (1997) have published a four-part critical review of foodborne disease surveillance. Part I (Guzewich *et al.*, 1997) describes the purpose and types of surveillance systems and networks. The listed components of foodborne disease surveillance are:

- Receiving notification of illnesses
- Investigating incidents and reporting findings
- Collating and interpreting data
- Disseminating information to effect control of current problems and provide guidance for prevention of disease.

This represents a fairly intricate system that requires well-coordinated activities at many levels, and its success depends upon the voluntary efforts of many participants. Unfortunately, foodborne disease investigations are sometimes poorly carried out, if at all, and the findings of investigations may be of insufficient quality for submitting reports and therefore remain in the office where the investigation was initiated. Recent reports on the incidence of foodborne diseases point to the difficulties in assessing the current status of foodborne morbidity and providing early warnings. Sample testing in the laboratory will help to overcome some of the deficiencies, as testing at the molecular level becomes more widespread.

Part II (Bryan *et al.*, 1997a) focuses on definitions and methods of tabulation of surveillance data, which can have a major influence on the way the data are analyzed and interpreted. For each step covered in disease investigation (time, space, dietary history, etc.), evaluations are made as to the value and limitation of data. The attempt of this part is to provide some degree of standardization, which is greatly needed.

Part III (Bryan *et al.*, 1997b) focuses on the food components, with collation of data listing vehicles, significantly important ingredients, places where foods were mishandled, methods of processing and preparation, and operations that contributed to outbreaks.

Part IV (Todd *et al.*, 1997) deals with the use of surveillance data, including:

- Developing new policies
- Evaluating effectiveness of programs
- Justifying food safety program budgets

- Modifying regulations
- Conducting hazard analysis and risk assessment, designing HACCP programs
- Informing the public about food safety
- Training food industry personnel
- Training public health officials
- Identifying new problems and research needs.

The goals of foodborne disease surveillance can only be fulfilled when the surveillance data reflect reality; this is presently not the case. Attempts have been made to estimate the degree of underreporting of foodborne diseases in the US (Bennett *et al.*, 1987; Todd, 1989), and these estimates have been revised by Mead *et al.* (1999) using more inclusive data sources. Mead *et al.* (1999) estimated that foodborne agents annually cause 76 million illnesses, 325 000 hospitalizations and 5000 deaths. The total number of foodborne illnesses reported through passive surveillance for 1993–1997 (Olsen *et al.*, 2000) was 86 058 with 29 deaths; about half of the outbreaks had an undetermined etiology. Table 1.1 shows a comparison between the estimates by Mead *et al.* (1999) and what was actually reported through passive surveillance

Table 1.1 Annual numbers of estimated and reported cases of foodborne illnesses per 100 000 persons in the United States

Agent	Estimation	Passive reporting
Norwalk virus	3274	0.09
<i>Campylobacter</i>	699	0.04
<i>Salmonella</i> , non-typhoid	478	0.32
<i>C. perfringens</i>	88	0.2
<i>Giardia lamblia</i>	71	0.003
<i>S. aureus</i>	66	0.1
<i>T. gondii</i>	40	–
<i>Shigella</i>	32	0.1
<i>Y. enterocolitica</i>	31	0.002
<i>E. coli</i> O157:H7	22	–
<i>E. coli</i> , enterotoxigenic	20	–
Rotavirus	14	–
Astrovirus	14	–
<i>Cryptosporidium parvum</i>	11	–
<i>E. coli</i> , non-O157 STEC	11	–
<i>B. cereus</i>	9.7	0.05
<i>E. coli</i> , other diarrhegic	8.5	–
<i>E. coli</i>	0.23	–
<i>Cyclospora</i>	5.2	–
<i>Vibrio</i> , other	1.8	0.01
<i>Listeria</i>	0.9	0.04
<i>Brucella</i>	0.3	0.007
<i>V. vulnificus</i>	0.02	–
Botulism	0.02	0.02
<i>V. cholerae</i>	0.02	0.0007
<i>T. spiralis</i>	0.02	0.007

Based on Mead *et al.* (1999) and Olsen *et al.* (2000).

(Olsen *et al.*, 2000). It is obvious that the incompleteness of passive reporting makes it impossible to use the data to represent the impact of foodborne disease on society. However, this should not be construed to imply that passive reporting is of no value: there is a lesson to be learned in each outbreak investigation when correctly performed, and passive surveillance will hopefully improve along the lines suggested by Guzewich, Bryan and Todd. It seems clear that an international standard of foodborne disease surveillance would be immensely valuable and make it possible to draw comparisons that are presently impossible. This in turn would provide new knowledge about causes of foodborne diseases. Because many of the activities in surveillance, especially those at the local level, are based on voluntary participation, it is important to maintain enthusiasm for the system. It is also important to improve the skills of those involved in conducting investigations and reporting results. The investigators must not only be familiar with the methodology of epidemiological investigation; they must also have knowledge of foodborne diseases and food production, processing and preparation.

4.1.2 Active surveillance

The inadequacy of passive surveillance gave impetus to establish sentinel studies, where the investigation of foodborne diseases can be performed in a more active fashion in limited geographical locations. Todd (1994) summarized some of these studies, which have been based on enrollment of local practitioners or have been epidemiological cohort studies where groups of people were interviewed about gastrointestinal disease syndromes at regular time intervals. These studies have yielded some surprising results in that disease incidence was much higher than expected.

In 1994 the Centers for Disease Control and Prevention (CDC) began implementing the Emerging Infections Program (EIP), in cooperation with selected state health departments, with foodborne diseases as a major component (CDC, 1996). The Active Surveillance Network (FoodNet) was established as collaborative effort among the CDC, the US Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the EIP sites (Centers for Disease Control and Prevention, 1997). The components of FoodNet are:

- Survey of clinical laboratories
- Survey of physicians
- Survey of populations by interviewing residents
- Case-control studies.

FoodNet began collecting population-based active surveillance data on culture-confirmed cases of seven foodborne infections (*E. coli* O157:H7, *Campylobacter*, *Listeria*, *Salmonella*, *Vibrio*, and *Yersinia*) in five EIP sites. The 2001 preliminary data include *Campylobacter*, *E. coli* O157:H7, *Shigella*, *Vibrio*, *Yersinia enterocolitica*, *Cryptosporidium parvum*, *Cyclospora cayatanensis*, and hemolytic uremic syndrome (HUS) in nine sites in the US, representing 37.8 million persons (CDC, 2002). During 2001, 13 705 laboratory-diagnosed cases were reported; the overall incidences of the different agents/syndromes are shown in Table 1.2. There were considerable differences in incidences among the different sites. California had more frequent isolations of *Campylobacter* and *Shigella* than any other site, while the Minnesota site had

Table 1.2 Overall incidence per 100 000 persons of infections/syndrome in nine sites of active surveillance – United States, 2001^a

Pathogen/syndrome	Incidence/100 000
<i>Salmonella</i>	15.1
<i>Campylobacter</i>	13.8
<i>Shigella</i>	6.4
<i>E. coli</i> O157:H7	1.6
<i>Cryptosporidium</i>	1.5
HUS ^b	0.9
<i>Yersinia</i>	0.4
<i>Listeria</i>	0.3
<i>Vibrio</i>	0.2
<i>Cyclospora</i>	0.1

^a CDC (2002)

^b Hemolytic uremic syndrome, usually caused by *E. coli* O157:H7.

the highest frequency of *E. coli* O157:H7, HUS, and *Cryptosporidium*. Among *Salmonella* isolates the dominating serotype was Typhimurium (15%), followed by Enteritidis (12%) and Newport (7%).

Not every isolation represents a case of foodborne disease, but Mead *et al.* (1999) have made estimates of the proportion of total cases that are foodborne. The estimates are 95% for non-typhoid *Salmonella* and 20% for *Shigella*. At the California site there were 14.3 isolations of *Salmonella* and 13.2 of *Shigella* per 100 000 persons; the adjusted numbers for foodborne cases become 13.6 isolations per 100 000 persons for *Salmonella* and 2.6 isolations per 100 000 persons for *Shigella*.

During the period 1996–2001, the incidence of most pathogens declined at the FoodNet sites. *Salmonella* declined by 15%, but there were differences among serotypes: Enteritidis and Typhimurium decreased, while Newport, Heidelberg, and Javiana increased. It has been suggested (CDC, 2002) that the decreases may be due to the implementation of egg quality assurance programs and improvements in hygienic manufacturing practices after the implementation of HACCP and performance standards in slaughterhouses.

Other active surveillance programs have been implemented. The Food Safety and Inspection Service (FSIS) *Salmonella* performance standards for slaughterhouses have been enforced since 1996, and programs directed at the primary production level and combined with intervention programs against *Salmonella* exist in Denmark and Sweden. Such programs are in principle not substantially different from control programs for tuberculosis or brucellosis, except that these two diseases affect not only humans but livestock as well.

4.2 Outbreak investigation

Outbreak investigations are at the core of foodborne disease surveillance, and the quality of these investigations is of utmost importance. The International Association of Milk, Food and Environmental Sanitarians (now the International

Association for Food Protection) published, in 1987, an extremely useful booklet on procedures for investigation of foodborne disease outbreaks; this booklet has been regularly updated, with the fifth edition appearing in 1999. Morse *et al.* (1994) have also described procedures, forms and tabulations used in investigation of foodborne diseases in New York State.

Although different authors and agencies promulgate or adopt somewhat different approaches to outbreak investigation, most outbreak investigations share the following key features:

- Receipt of an initial report or data
- Verification of the diagnosis
- Determination of whether an outbreak has occurred
- Search for additional data and cases
- Description of cases in terms of time, space and persons
- Formulation of hypotheses
- Further analytical, epidemiological, environmental, and laboratory studies
- Synthesis of findings with conclusions and recommendations
- Control measures
- Written reports.

When the outbreak is relatively confined in terms of time, space, and the size of the population at risk (as in some common source outbreaks), the preferred epidemiologic investigation method is the retrospective cohort study, where the fates of people who ate the putative food are compared to those of the people who did not. A cohort is an assemblage of individuals who share one or more characteristics that in turn define its membership – for example, being present at an event where a temporally defined foodborne outbreak occurred. In the special case of an outbreak investigation, we further define the cohort as being *closed* in the sense that there can be no immigration or emigration of its membership once the temporal definition of the cohort is established. Members of the cohort may be *censored*, meaning that they are lost to follow-up or are precluded from developing the disease due to competing causes. The validity of a cohort study rests on the assumption that censoring is: (a) unrelated to disease incidence, and (b) unrelated to the exposure(s) under study. Because the reasons for censoring are often unknown, the former assumption (a) is difficult to verify, so it is critical that the number of censored individuals be kept as minimal as possible. Conscientious and assiduous efforts at tracing back and establishing contact with all the members of the cohort are instrumental in preventing censoring bias.

Another assumption underlying the success of undertaking a cohort study to investigate a disease outbreak is that there is a distribution of exposure to the causative agent/source among the people in the cohort, allowing the comparison of disease incidence conditional on exposure status. The absence of a distribution, which could occur if everyone in the cohort consumed the putative source of an infectious organism, precludes the determination of comparative measures of exposure-specific disease incidence. The mere finding that all diseased individuals consumed a particular food or drink is not necessarily sufficient to implicate that consumable. To illustrate this point, suppose at a dinner gathering of people a particular salad was contaminated.

If everyone ate the contaminated salad, and 75% of the individuals developed the disease, then the salad would seemingly be implicated. Suppose, however, that everyone also drank the same water and ate several of the other foods offered: 75% of these individuals would also develop disease. Thus, there would be no epidemiologic basis by which investigators could distinguish the potential responsible food or drink from incidental ones without ancillary information.

The aforementioned example illustrates the need for a coherent way to evaluate data collected in the course of doing cohort studies. Suppose that we undertake a cohort study of an outbreak of an intestinal disease at a single-day gathering and collect retrospective information about all foods and drinks consumed by the individuals present. For simplicity, we shall assume that there was no loss to follow-up of any of the members of the cohort, that any consumption of a food is considered to be a positive food intake exposure (obviating the need retrospectively to measure quantities of items consumed), and that there is no misclassification of an individual's disease status. Individuals can then be cross-classified by their binary exposure and by their binary disease status.

The assumptions above are sufficient to allow the calculation of the proportion of individuals in the cohort that develop disease (*incidence proportion*), both crudely and conditional on exposure status. Although a cohort study is by definition non-experimental, the unexposed group in a cohort study is analogous, though not identical in construct, to the control group in an experimental study. However, it is important to appreciate the distinction between the two study types: in an experimental study exposure is typically randomized to ensure comparability between the study groups, while in a non-experimental study subjects typically select their own exposure for reasons unknown but that may be causally important. To illustrate, an individual on antibiotics may be both more susceptible to developing enteric disease, and also specifically avoid certain foods, making such foods appear risk-protective. The absence of randomization, then, can be a serious impediment to cohort study validity. The reasons why individuals select their own exposures are examples of confounders – variables that lead to a biased (i.e. invalid) statistic. Although it is possible to obtain valid statistics derived from incidence proportions through analytic control of confounding, this subject is beyond the scope of this chapter; a more thorough discussion of confounding may be found in Rothman and Greenland (1998).

The incidence proportion among individuals exposed to a particular food can be designated by the following notation:

$$P(D|E)$$

where P = disease probability (i.e. the proportion of individuals that get the disease), D = development of disease, and E = the conditional status of being exposed. Similarly, we can write the incidence proportion among unexposed individuals as:

$$P(D|\bar{E})$$

where \bar{E} = the conditional status of being unexposed. A parameter that is causally interpretable (in the absence of any biases) as the proportionate change in the average

risk of disease moving from non-exposed to exposed status is the *incidence proportion ratio (IPR)*, denoted by:

$$\frac{P(D|E)}{P(D|\bar{E})}$$

When based on observed data, the IPR statistic is extremely useful in distinguishing causal foods from non-causal foods in investigating disease incidence during an outbreak. If a particular food was not contaminated, and its consumption was independent of any food that was contaminated, then the incidence proportion of disease among those who ate the food would be expected to be approximately equal to the incidence proportion of disease among those who never ate the food, and the IPR would be approximately equal to 1.0. Formulae for variance estimators and confidence intervals of the crude IPR, and tests of the null hypothesis that the crude $IPR = 1$ are available (Rothman and Greenland, 1998); these formulae generally require the construction of contingency tables cross-classified by disease and exposure frequencies.

It is also possible to take the difference between the exposure-specific incidence proportions, rather than the ratio above, leading to the calculation of the *incidence proportion difference (IPD)*:

$$IPD = P(D|E) - P(D|\bar{E})$$

Under the null hypothesis of no effect of a consumed food, the expected IPE = 0. Although the IPD can vary between -1 and 1 , in practice it is unlikely that foods protect against foodborne disease, hence the IPD should fall between 0 and 1 . Although the magnitude of the IPD is constrained by the incidence proportion among the unexposed (a characteristic from which the IPR does not suffer), virtually all foodborne diseases would have such a low background incidence during the finite period of an outbreak investigation that this should not be an impediment to causal analysis. As with the IPR, the IPD has its own formulae for variance estimation, a confidence interval, and a test of the null hypothesis that the $IPD = 0$ (Rothman and Greenland, 1998).

When it is not possible clearly to enumerate the constituents of a cohort during an outbreak, particularly those that did not develop disease and hence were not reported, or when the cohort is so large that gathering retrospective information on everyone in the cohort is impractical, the epidemiologic design of choice is generally the case-control study. While these can be used to study foodborne disease outbreaks when cohort studies are not feasible, they are better suited to studying sporadic disease, and will be discussed in more detail in the following section.

4.3 Investigation of sporadic cases of foodborne diseases

4.3.1 Measures of effect

From the standpoint of causal identification of substances contributing to foodborne disease, the ability to conduct a cohort study offers a distinct advantage over other study designs; notably, the ability to estimate exposure-specific risks

and their conjunctive effect measures. However, the conditions under which a cohort study can be conducted are highly restrictive: there must be a way of inventorying the members of the cohort defined by time and space; the period of the outbreak must be relatively brief, with a rapid rise in the incidence of the disease, followed by a relatively quick return to an endemic level; censoring must be minimal and unrelated to exposure and disease status; and the morbidity must be high enough for the epidemic to be recognized.

The vast majority of diseases transmitted by food or water, however, fail to fulfill most, if not all, of these criteria. Most foodborne disease that comes to the attention of public health officials occurs in a sporadic and seemingly random temporal and spatial pattern. Such sporadic incidence is consonant with either the occurrence of etiologically unrelated and isolated cases or with a paucity of cases eventually diagnosed and reported from one or more unrecognized epidemics. The latter represents an extreme case of censoring in which almost all diseased individuals are unaccounted for and hence lost to follow-up. What led these individuals from an epidemic to become ill is immaterial, and no outbreak investigation of them is possible; they cannot be practically studied as part of a larger cohort because none could be enumerated. Furthermore, it often takes a considerable amount of detective work to identify the vehicle/source outbreaks that do not involve a common source in a restricted time and space, especially if the incubation period of the agent is long or the food is distributed through different channels at different periods of time.

The solution to how to study determinants of sporadic foodborne infection requires an appreciation that so long as exposure-specific risks are unnecessary to know, case-control studies offer efficient alternatives to conducting cohort studies while still yielding ratio measures of effect. Indeed, it would be a mistake to consider case-control studies as distinctly different from cohort studies; the designs are distinguished by whether sampling of the population at risk occurs, as it does in case-control studies, or whether the population at risk is inventoried in its entirety, as in cohort studies. Due to the necessity of sampling based on outcome status (conventionally diseased or non-diseased subgroups), case-control studies are unable to provide estimates of disease incidence without ancillary information not usually collected or readily available for foodborne illnesses. By conditioning on outcome status, investigators can only measure the probability distribution of exposure(s) in the respective study groups (e.g. the proportion of cases or controls that are exposed to a particular food):

$$P(E|D) \text{ and } P(E|\bar{D})$$

where D and \bar{D} represent cases and controls, respectively.

It is important to recognize that these two distributions (and their ratio), where exposure is an ‘outcome’ of disease rather than a cause, are not quantities of intrinsic causal interest. It is illogical to consider how disease status can ‘affect’ the distribution of prior exposures because of the inverse temporal relationship. The distributions have intrinsic value, nevertheless, when transformed into exposure odds, defined

as the probability of each level of exposure divided by its converse probability, such that the numerator and the denominator of the exposure odds sum to one:

$$P(E|D)/(1 - P(E|D)) = P(E|D)/P(\bar{E}|D), \text{ and}$$

$$P(E|\bar{D})/(1 - P(E|\bar{D})) = P(E|\bar{D})/P(\bar{E}|\bar{D})$$

The first statement is called the exposure odds among cases, and the second is called the exposure odds among controls. The ratio of these two odds is the well-known exposure (case-control) odds ratio:

$$\frac{P(E|D)/P(\bar{E}|D)}{P(E|\bar{D})/P(\bar{E}|\bar{D})}$$

Like its components, the exposure odds ratio has no natural causal interpretation. However, it is possible to show using Bayes theorem that the exposure odds ratio is algebraically and numerically equivalent to the incidence (disease) odds ratio:

$$\frac{P(D|E)/P(\bar{D}|E)}{P(D|\bar{E})/P(\bar{D}|\bar{E})}$$

Although the exposure odds ratio and the incidence odds ratio are interpretively different, the significance of their algebraic equivalence should not be minimized: it provides the fundamental basis for the legitimate use of case-control studies in causal inference.

Odds ratios derived from case-control studies are difficult to literally interpret because, unlike probabilities that have a domain of 0 to 1 inclusive, the domain of odds lies in the interval of 0 to infinity. However, as we will show, most case-control studies of foodborne disease can be designed so that the exposure odds ratios can be interpreted as other, more easily understood ratio measures of effect. The most important – and controversial – issue in designing a case-control study of sporadic foodborne disease is how the controls are selected.

4.3.2 Cumulative incidence case-control studies

For the reasons presented above, it is not always practical to conduct a cohort study in the investigation of a foodborne disease outbreak. Although a cohort may in fact exist and can be enumerated, censoring can prevent the calculation of exposure-specific incidence proportions, and hence any derivative effect measures. When a common source is suspected of transmitting the totality of short-term disease in the cohort, it is still possible to test this hypothesis using a *cumulative incidence case-control study*.

As in other case-control studies, cases with foodborne disease are compared to controls that did not develop foodborne disease. Unlike other types of case-control studies, however, controls are sampled from those members of the cohort who remained disease-free throughout the entire duration of the outbreak. By definition, then, controls in this type of case-control study are not eligible to become cases because they are only selected after the outbreak is over.

Cornfield (1951) demonstrated that the exposure odds ratio from a cumulative incidence case-control study has attractive statistical properties when the conditional

incidence of disease is assumed to be rare (i.e. less than 5%). Under this restriction, the case-control odds ratio remains quantitatively equivalent to the incidence odds ratio, but now the incidence odds is approximately equal to the incidence proportion, i.e.

$$\frac{P(D)}{P(\bar{D})} \cong P(D)$$

This property, ubiquitously known in the epidemiologic lexicon as the *rare disease assumption*, leads to the powerful conclusion that the case-control odds ratio may be interpreted as the incidence proportion ratio. It is important to recount that it is not sufficient for this assumption to hold overall (unconditionally); it must also be met marginally and jointly conditional on all levels of exposures (foods) and strata of confounders (e.g. age groups, gender, HIV status etc.). Unfortunately, it would be surprising if this assumption was not violated in an outbreak investigation; depending on the dose of a foodborne pathogen, the morbidity associated with consumption of a contaminated food could be quite high. Therefore, caution must be exercised in the interpretation of the odds ratio, so as not to confuse odds with concepts such as probability, risk or likelihood.

Validity in a cumulative incidence case-control study of a foodborne outbreak depends on an assumption of random sampling – i.e. the enrolled cases being representative of all cases, and controls being representative of all non-diseased individuals. If the reasons why individuals cannot be located or refuse to participate are somehow related to the foods that they ate, then bias can result. Although a minimum of one control should be located for each enrolled case (for reasons of statistical efficiency), this may not always be possible when morbidity is high. Nevertheless, as long as resources exist for obtaining information in an outbreak investigation, there is no virtue in not making an effort to locate as many controls (and cases) as possible: approximately half of all outbreak investigations fail to implicate a cause, underscoring the difficulty in successfully undertaking retrospective studies. Investigators should also be cognizant that cases may be more motivated to recall a complete dietary history during an outbreak compared to controls. To the extent that investigators can obtain documentation of all consumables available during an outbreak, such a listing can be used to establish prior food intake during interviews to minimize lack of recall, rather than asking individuals to volunteer what they remember eating. Although some error in recall is to be expected, it would not be surprising to have some controls recall eating food found to be contaminated – not because of error in recall or high endemic level of disease, but because the quantity of a food eaten may serve as a proxy for the number of pathogenic organisms consumed. Similarly, cases may not recall eating a contaminated food, but could have still been exposed to an infectious dose through unrecognized cross-contamination. Though investigations such as this assume heterogeneity of the at-risk population, they generally assume homogeneity of distribution of the pathogen in the suspect food. Exceptions, in which the infectious agent or toxin is localized in part of a lot of food, are common and will surely complicate epidemiological analysis.

4.3.3 Incidence density case-control studies

Although the prototypical epidemiologic study of foodborne disease is the outbreak investigation, most cases that occur in large populations are seemingly unrelated and sporadic. The study of such cases is not performed for the purpose of determining a contaminated food that is in all likelihood long discarded. Instead, research into the determinants of disease in sporadic cases is performed for enhancing public health through disease prevention. Such work has as its underlying goal the development of a better understanding of what actions individuals took that placed themselves at heightened risk of foodborne disease, and what host characteristics they had that predisposed them to succumbing to infection or intoxication. To illustrate this concept, consider that much of the poultry sold to consumers in the US is contaminated with enteric pathogens including *Campylobacter* and *Salmonella*. Yet most people who consume poultry do not develop illness from it. The salient issue is not about whether poultry is contaminated, and if so with what pathogen, but rather is a contrast of what individuals who ate poultry did or did not do that influenced whether they developed disease or not. When endemic contamination of consumer foods is ubiquitous in large populations, the identification of such behaviors can lead to preventive health strategies that if adopted and implemented can profoundly affect disease morbidity. Such strategies can include education, identification of individuals at heightened risk, improved food hygiene at the post-harvest level, avoidance of certain drugs that affect host defenses, etc.

Public health officials typically collect information from reported cases about risk factors related to foodborne disease, though they generally lack the resources necessary to conduct the controlled studies that could identify the characteristics and behaviors that contributed as component causes to the development of disease. Such studies are difficult to perform because, unlike the situation of an outbreak investigation where a cohort can often be clearly defined, sporadic cases arise in large populations that are dynamic in membership and defy enumeration short of through a census. Clearly, cohort and cumulative incidence case-control studies are inappropriate for studying sporadic cases.

Instead, researchers can rely on an alternative study design: the *incidence density case-control study*. Over an extended but closed period of time, cases are recruited and studied, retrospectively, prospectively or both (ambispectively), from a large population. Case ascertainment may occur at local health agencies (where mandatory reporting occurs), at hospitals (where a confirmatory disease diagnosis is made) or at laboratories (where isolation of organisms or toxins occurs). To be sure, such cases can hardly be described as typical of all cases that occur but remain undiagnosed: study cases are generally more severely affected, more likely to utilize medical services, and preferentially patronize medical personnel who are willing to obtain a diagnosis instead of solely treating symptoms. This select group of patients may or may not be representative of the larger but unrecognized body of individuals with foodborne disease with respect to behaviors and host characteristics. In general, if disease severity is associated with the presence of risk factors, then the problem of lack of representativeness and generalizability is offset by the inclusion of individuals in a study that will make it easier to identify such risk factors. If severity and the other

imponderable factors that lead an individual to seek diagnosis and treatment are unassociated with risk factors, the lack of representativeness is no longer an issue.

Just as cases are recruited throughout the study period, controls are selected from the population at risk during the identical period. This method of sampling controls distinguishes incidence density sampling from cumulative incidence sampling: in the former, controls are eligible to become cases after being sampled as controls, and would be included in the study separately as both a case and as a control. Although controls can be randomly selected from throughout the study period, it is preferable to select controls at approximately the same time that cases occur, creating matched sets of, typically, one case and one or more controls. When a matched analysis is performed using stratified analysis or conditional logistic regression, any confounding by time will be controlled for. This study design also yields case-control odds ratios but, unlike cumulative incidence case-control studies, these odds ratios are interpretable as *incidence rate ratios*: the proportionate change in the incidence rate of disease moving from unexposed to exposed status. The gravity of this interpretation should be appreciated – it allows the case-control odds ratio to estimate a readily understood measure of proportionate change in the disease rate even when the disease is not rare. In other words, even in the absence of the rare disease assumption, an incidence density case-control study need not be interpreted in terms of relative odds. Furthermore, when the disease is rare, the incidence density case-control odds ratio is a superior estimator of the incidence proportion ratio, compared to the cumulative incidence case-control odds ratio (Greenland and Thomas, 1982).

Control selection in incidence density case-control studies of foodborne disease is neither trivial nor uncontroversial. Controls are sampled to reflect the exposure distribution in the source population (at risk) of cases; *selection bias* arises when there is a disparity in this distribution between the control and source populations. When cases emanate from a large population and are obtained from a disease registry, it is often efficient to take a primary sample of the source population. The latter can be performed through standard survey protocols, such as random digit dialing, neighborhood interviews, etc. For example, one study of determinants of sporadic salmonellosis was performed by obtaining cases from county health departments, which maintain vital information on patients with reportable diseases (Kass *et al.*, 1992). Controls were selected through random digit dialing of the counties that reported to their respective health departments that provided cases. Although this method of sampling is relatively straightforward, caution must be exercised that the method of obtaining controls is unrelated to the distribution of risk factors in the source population. For example, if individuals in lower socioeconomic strata are less educated about proper food preparation techniques and are also less likely to own a telephone, then a random digit dialing survey would not capture such individuals and hence would underestimate the prevalence of improper food-handling skills.

An alternative control sampling procedure is often employed when cases are obtained from hospitals. Although it is uncontroversial to locate cases with a foodborne illness in this way, it is unclear what the source population of such cases is; indeed, such a population may be only a hypothetical construct. Although some hospitals have a monopoly on medical care for a defined region, it is also common

for other hospitals to serve as referral centers for patients living both far and near from them. Patients at such hospitals may not necessarily be representative of all patients in the source population, even if they are a census of cases that are seen at those hospitals. In this scenario of a hospital-based study, a key requirement for control selection is that the control, had she or he developed the foodborne disease under study, would have entered the hospital and been diagnosed with the disease through exactly the same mechanism as the cases were. This underlying tenet of control selection is important to adhere to because the reasons why certain individuals patronize specific hospitals could in some unknown or unspecified way be related to the risk factors under study. For example, if hormone replacement therapy is via immune modulation, a possible risk factor for enteric infection, and one region hospital is recognized for its treatment of postmenopausal women, then patients under such therapy may preferentially attend that hospital over another. For this reason, controls are typically selected from the same hospitals as cases, and from patient diagnostic groups that would be more likely to also be seen at the same hospital for gastrointestinal foodborne illness. To illustrate this point, it is plausible that, if patients had an infectious respiratory disease at a hospital, if they later developed an infectious gastrointestinal foodborne disease they would present themselves to the same hospital. In contrast, a group of cancer patients would be ill-advised as a control group, because such patients often gravitate to certain tertiary care facilities known for prowess in treating such conditions, and such patients may be atypical of the source population with respect to their distribution of risk factors.

There are additional considerations when selecting a control group for a hospital-based case-control study. It is essential to recognize that, regardless of what disease or group of disease diagnoses is used to constitute such a control group, the risk factors under study must *not* be determinants of these control diagnoses. Were this to occur, the distribution of the exposure(s) in the controls would be unrepresentative of the source population, and in fact would be spuriously closer to the distribution of the exposure(s) in the cases, leading to case-control odds ratios that were biased towards the null value of 1.0. As an illustration of this, consider a case-control study to determine whether individuals taking oral antibiotics are at higher risk of developing *Campylobacter*, *Salmonella*, and *E. coli* infections. While the case definition is obvious with confirmatory stool cultures, the control definition is less transparent. Patients who had been treated for other infectious diseases would pointedly not be appropriate as controls because such individuals are likely to have been exposed to oral antibiotics to an extent clearly higher than that of the source population of cases. Failure to recognize such associations would result in effect measures not only being biased towards the null, but could even lead to factors that are harmful appearing to be protective (or *vice versa*).

This admonition should never be construed to mean that controls should be selected because they are unexposed; any such study would be fatally flawed from its inception. The key central theme is that controls should not be *selected* on the basis of their exposure status, or of a proxy of exposure. In the above example, treatment for infectious disease was a proxy for antibiotic use. On the other hand, if individuals treated for closed fractures and ligament or tendon damage were selected as controls

(under the assumption that these conditions are not treated with antibiotics), then even if these controls were taking antibiotics for other ancillary medical reasons they could remain in the study as controls because their control selection did not depend on the other reasons.

Findings from such case-control studies should be interpreted with respect not only to the odds ratios or incidence rate ratios, but also to baseline (unexposed) rates. The reason for this is that even factors that exert large *proportional* effects on disease rates may be of negligible public health importance if their baseline disease rates are low and the factors are rare in the population at risk. In other words, overall morbidity in a population is a function of not only the relative effect of a factor, but also its prevalence in the population. For this reason, weaker risk factors can exert a greater influence on disease incidence if they are relatively common than stronger risk factors that are relatively rare. It makes little sense to conduct studies of risk factors if their effect on morbidity is small or they are not subject to mitigation through education or public health interventions.

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