Long-term sequelae to foodborne disease

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Summary
Most of the concern about foodborne disease has been focused on the immediate effects of acute infection. Recent information has shown that many of these foodborne infections also have long-term sequelae with serious health effects and a significant economic impact. To increase the awareness of animal health professionals to these sequelae, the authors discuss two groups of sequelae which are strongly associated with preceding infection (reactive arthritides, including Reiter's syndrome, and the Guillain-Barré syndrome) as well as the possible association between Crohn's disease and Mycobacterium paratuberculosis. The discussion includes a description of the disease syndromes along with epidemiological and economic information. More reliable epidemiological and economic data on chronic sequelae to foodborne disease will be needed for future evaluation of the cost-effectiveness of mitigation strategies to reduce the occurrence of foodborne pathogens.

Keywords

Introduction
Foodborne diseases exact a considerable toll on public health. In the United States of America (USA) alone, the best estimates suggest between 6 million and 33 million cases of foodborne disease and up to 9,000 foodborne disease-related deaths annually (8). The most noticeable manifestation of foodborne disease is acute illness characterised by symptoms which may include diarrhoea, cramps, fever and vomiting. For the elderly, the very young, and other groups of immuno-compromised people, the risk of death from foodborne disease is significantly higher than for healthy individuals. In addition to acute illness and death, less well-known but significant impacts of foodborne diseases are long-term sequelae to infections created by pathogens frequently acquired through exposure to contaminated foods. Although the data on long-term complications to foodborne diseases are not collected and disseminated systematically, evidence suggests that the economic effects of these complications may exceed the costs of acute illness (2).

The authors seek to increase the awareness of animal health professionals to the variety, health significance and economic impacts of long-term sequelae to foodborne diseases. With increasing awareness and understanding of these problems, the effects and possible mitigation approaches can be incorporated into the emerging practice of quantitative risk analysis in food safety. The discussion is focused on bacterial pathogens which are spread from food animals to man. To illustrate the diversity and significance of these complications, three of the better-known examples are discussed, as follows:

a) reactive arthritides from enteric pathogens

b) Guillain-Barré syndrome associated with Campylobacter jejuni exposure

c) Crohn's disease and the possible association with Mycobacterium paratuberculosis in cattle.

For the sake of brevity, foodborne parasites and viruses are not included in the discussion, although these too can create significant complications (8). In particular, the effects of congenital toxoplasmosis infection are particularly serious and generate a high rate of impairment in exposed individuals, with attendant life-long economic costs (13).
Reactive arthritis from enteric pathogens

The discomfort and inconvenience of diarrhoea and vomiting associated with acute infection by organisms such as Salmonella (in particular S. Enteritidis and S. Typhimurium), Campylobacter jejuni, Shigella sp. and Yersinia are well-known; the frequency and seriousness of the long-term complications associated with these pathogens are not as well documented. Infections from these organisms appear to give rise to a number of chronic joint diseases which include reactive arthritis, Reiter's syndrome and ankylosing spondylitis (18). In these sterile, reactive arthritides, the triggering organisms are not found in the affected joints and no rheumatoid factor is present, but elevated antibody levels to these organisms are present in the host (16).

Symptoms commonly begin approximately 7 to 30 days after an intestinal illness. The knee is often infected along with other peripheral joints. Reiter's syndrome, considered a special case of reactive arthritis, typically includes three symptoms: asymmetric arthritis (joints on opposite limbs are affected) in knees and ankles, a non-specific urethritis and conjunctivitis. The duration of symptoms varies considerably, but in most individuals, symptoms subside in less than six months. However, some individuals may take in excess of one year to recover fully, and a significant portion of affected persons suffer persistent or relapsing illnesses. In addition to environmental factors, genetic factors play a significant role in the development of the reactive arthritides following exposure to a triggering organism. Approximately 6%-10% of white Americans, 2%-3% of African Americans and 1% of Japanese people carry the gene for susceptibility (18). A recent review of foodborne diseases reported that approximately 2%-3% of all exposed individuals develop one of the reactive arthritides (8). However, approximately 20% of exposed susceptible individuals will develop one of the reactive arthritides, with Reiter's syndrome occurring ten times less frequently than reactive arthritis (2).

Detailed epidemiological investigations of several foodborne disease outbreaks suggest that these rates may understate the true number of cases and the associated economic impact of reactive arthritides due to foodborne disease. An outbreak of Salmonella Enteritidis among physicians found that 108 of 113 (95.6%) exposed patients were developing salmonellosis; of the 108 ill people, 17 (15.7%) subsequently developed one of the reactive arthritides (10). In another outbreak involving 116 people who became ill due to Salmonella Typhimurium, 16.4% of those ill developed reactive arthritis and 9.4% developed conjunctivitis (15). Nearly 40% of those with reactive arthritis had symptoms which persisted for over one year. The attack rate for reactive arthritis among exposed persons in these outbreaks is 7 to 8 times higher than the generally reported rate (2%-3%). Unfortunately no recent, comprehensive analysis of the economic impact of these diseases is available in the literature; however, the effects are discussed by Archer and Kvenberg (1) and Archer and Young (2). Smith et al. estimated that 100,000 to 200,000 cases of reactive arthritis arise from foodborne infections each year in the USA (18).

Guillain-Barré syndrome and Campylobacter jejuni infection

Campylobacter jejuni is commensal in the intestinal tracts of birds; thus, as a foodborne disease pathogen, infection is most often associated with poultry (17). This pathogen is the most common source of foodborne illness in the USA (19). Unlike organisms such as Salmonella, C. jejuni is not well known to the general public, in part because the organism was not identified as a human pathogen until the 1970s, when the culturing techniques enabling isolation were developed (16).

The Guillain-Barré syndrome (GBS) is an acute, progressive neuropathy which is characterised by paralysis, pain, muscular weakness and distal sensory loss. In severe cases, respiration, swallowing, eye motion and autonomic functions may be affected. Patients are often bed-ridden because of paralysis and mechanical pulmonary support may be required; most patients are hospitalised (17). The disease progresses rapidly, sometimes within the course of a single day, although symptoms sometimes take several weeks to develop. Most patients experience the worst symptoms within a month of disease onset and then recover slowly. The rapidity of disease onset, the severity of the symptoms and the persistence of these symptoms make GBS a particularly devastating illness. Case-fatality rates reported in the literature range from 2% to 8% (3, 11). Since the decline in polio following widespread public vaccination campaigns, GBS is the leading cause of acute flaccid paralysis throughout the world (11). The syndrome can probably arise from a number of viral and bacterial infections, as well as administration of certain drugs and vaccinations (14). C. jejuni is recognised as the most common preceding infection (11).

Epidemiological studies have highlighted the relationship between GBS and disease resulting from preceding C. jejuni infection. A case-control study of 103 patients with GBS or Miller-Fisher syndrome (a variant of GBS) presented in England and Wales between 1992 and 1994 showed that 26% had preceding C. jejuni infection (12). The study found that preceding infection with C. jejuni was associated with neurological degeneration, slow recovery and severe residual disability compared to GBS patients without preceding infection. Prior C. jejuni infection was significantly associated with poor outcome, even after correcting for other factors indicating poor prognosis. Another recent study conducted in...
the United Kingdom of 79 patients with GBS showed that one year after the onset of disease, 8% of the patients had died, 4% were still bed-ridden and 9% were still unable to walk without assistance (11).

The medical costs of GBS associated with C. jejuni infection have been investigated more fully than other long-term sequelae of foodborne diseases. A recent report estimates that of the 2,600 to 9,500 new cases of GBS which occur annually in the USA, between 525 and 3,800 are triggered by infection with C. jejuni (3). The annual costs of C. jejuni-associated GBS are estimated at US$0.2 to US$1.8 × 10^6 in the USA. By comparison, the annual economic impact of acute campylobacteriosis was estimated at US$1.3 to US$6.2 × 10^6, which means that long-term sequelae to C. jejuni are of the same magnitude as the costs of acute illness, despite the fact that the long-term complications are at least 100 times less common.

Crohn’s disease in humans and Johne’s disease in cattle

Although there is strong evidence showing causal links between foodborne pathogens and the conditions discussed above, the link between Crohn’s disease and Mycobacterium paratuberculosis is less strong. The cause of Crohn’s disease remains unknown (4, 21). Researchers are investigating several possible agents and conditions but there have been no definitive results. If M. paratuberculosis were proved to be the cause of Crohn’s disease, foodborne exposure would probably be the major source of human contamination.

Mycobacterium paratuberculosis is the causative agent for Johne’s disease in cattle, sheep and goats. Johne’s disease is a chronic granulomatous intestinal infection of the ileocaecal region of the intestine (9). Animals are often infected at a young age through exposure to faeces from cattle shedding the organism. The clinical signs of Johne’s disease – persistent diarrhoea and weight loss – may not be revealed until two to five years after infection. Johne’s disease is reported in every country in the world with animal agriculture and adequate laboratory facilities for diagnosis. In the USA, 5%-10% of dairy cattle are infected with M. paratuberculosis, and up to one third of herds in Wisconsin showed serological evidence of infection in 1994 (6).

Crohn’s disease in humans is displayed as a chronic granulomatous enteritis very similar to Johne’s disease in cattle. In the 1980s, researchers reported an occasional isolation of M. paratuberculosis from patients with Crohn’s disease (4, 21). Standard culture techniques for mycobacteria proved inefficient in isolating M. paratuberculosis because the bacterium often occurred as cell-wall deficient (called spheroplasts). These spheroplasts fail to survive standard culturing techniques. There is also a possibility that the spheroplast form of M. paratuberculosis would not be noticed in tissue samples used for histopathology. Other methods of detection, such as polymerase chain reaction and genetic probes, are currently used to detect M. paratuberculosis. Many researchers have performed case-control studies to compare the prevalence of M. paratuberculosis in Crohn’s disease patients and controls. These studies have shown prevalence rates ranging from 40% to over 75% in the Crohn’s disease patients compared to 0% to 25% in the controls. However, other researchers found no significant difference in the prevalence (6).

While the research does not prove a causal association between M. paratuberculosis and Crohn’s disease, there appears to be substantial proof to show an association, at least for a substantial proportion of the Crohn’s disease patients. If a causal link was proved, public health officials would have to re-evaluate current management of Johne’s disease, particularly in dairy cattle.

Cattle infected with Johne’s disease can shed the bacterium in faeces and milk, thus M. paratuberculosis is often present in raw milk, either directly or indirectly through faecal contamination (20). Recent research has suggested that M. paratuberculosis is more closely related to the M. avium complex than to other mycobacteria. This is significant because both M. paratuberculosis and M. avium are more resistant to pasteurisation time and temperature criteria than other milk-borne pathogens (5). Current pasteurisation methods may not kill all M. paratuberculosis organisms present in milk, which is of particular importance when considering that approximately one third of the cheese produced in the USA is derived from unpasteurised milk (6).

When Johne’s disease is diagnosed in a cow on a dairy farm, the standard recommendation is to send the animal to slaughter. In the late stages of the disease, M. paratuberculosis may be spread systematically throughout the animal (7). Most of these culled dairy cows pass ante-mortem inspection and enter the slaughter system for production of ground beef. Whether by systemic infection or contamination from faeces, these cattle pose a great risk for contamination of the final product (ground beef) with M. paratuberculosis (6).

Research is ongoing to determine whether M. paratuberculosis in the food supply poses a health risk to humans, either through Crohn’s disease or some other manifestation. If a link is ever proved, current systems for producing milk and meat will have to be re-evaluated to determine whether more effective mitigation measures are needed to reduce exposure to this bacterium.
Conclusion

In addition to the well-known symptoms and associated impact of the acute form of foodborne diseases, a number of bacterial, viral and parasitic pathogens can cause long-term sequelae which are perhaps more economically significant than the effects of acute disease. The long-term sequelae impose significant costs on individuals, families and communities. The sheer magnitude of the impact associated with these long-term sequelae invites additional analysis and research to determine whether cost-effective mitigation strategies can be developed to reduce the occurrence of these diseases.

Séquelles chroniques des toxi-infections alimentaires
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Résumé
S'agissant des toxi-infections alimentaires, ce sont les effets immédiats de l'infection aiguë qui ont été le plus étudiés jusqu'à présent. Or, des informations récentes montrent que nombre de ces toxi-infections alimentaires entraînent également des séquelles à long terme, avec des conséquences graves sur la santé et une incidence économique considérable. Pour mieux sensibiliser les responsables de la santé animale à ce problème, les auteurs décrivent deux types de séquelles qui sont étroitement associées à une toxi-infection antérieure (les arthrites réactionnelles, dont le syndrome de Reiter, et le syndrome de Guillain-Barré) ainsi que le lien éventuel entre la maladie de Crohn et Mycobacterium paratuberculosis. Ils décrivent ces syndromes, ainsi que leur épidémiologie et leur incidence économique. Des données épidémiologiques et économiques plus précises sur les séquelles chroniques des toxi-infections alimentaires devraient permettre d'évaluer la rentabilité des stratégies visant à réduire la fréquence des agents pathogènes transmis par les aliments.

Mots-clés

Secuelas prolongadas de toxi-infecciones alimentarias
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Resumen
Hasta hace poco, la atención acerca de las toxi-infecciones alimentarias se centraba en los efectos inmediatos de las infecciones agudas. Sin embargo, algunos datos recientes han puesto de relieve que las toxi-infecciones alimentarias producen también secuelas a largo plazo, con graves efectos sobre la salud y un importante impacto económico. Con objeto de sensibilizar a los profesionales de la sanidad animal sobre la importancia de esos efectos a largo plazo, los autores examinan dos grupos de secuelas estrechamente relacionadas con previas toxi-infecciones (las artritis reactivas, incluyendo el síndrome de Reiter, y el síndrome de Guillain-Barré), así como la posible relación entre la enfermedad de Crohn y Mycobacterium paratuberculosis. Además de la descripción de cada uno de los síndromes, se aporta información sobre sus consecuencias epidemiológicas y económicas. Para evaluar con exactitud la
relación costo/efectividad de las estrategias para reducir la frecuencia de patógenos en los alimentos, será necesario disponer de datos epidemiológicos y económicos más detallados sobre las secuelas crónicas de las toxifi- infecciones alimentarias.

**Palabras clave**


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**References**