Emerging Trends in Foodborne Diseases

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KEYWORDS

• Foodborne infections • Outbreak investigations • Laboratory diagnosis
• Molecular subtyping • Trends • Imports • Burden of illness • Food poisoning

KEY POINTS

- About 1 in 6 (or 48 million) Americans become ill with a foodborne illness each year.
- Successful food safety interventions significantly decreased rates of some foodborne illnesses before 2005.
- Progress in decreasing rates of foodborne illness has stalled; *Salmonella* infection rates are the same as in 1998.
- Public health surveillance, outbreak detection, and investigation serve to focus prevention efforts.
- Clinicians play a critical role in linking clinical observations and findings with public health action.

WAS IT SOMETHING I ATE?

Infections transmitted through foods are common. Presenting with a variety of symptoms and syndromes, these infections complicate school, work, and travel and can lead to hospitalization and even death, particularly in high-risk patients. The spectrum of infections and the food sources that transmit them has changed as new pathogens have emerged or are better detected, the number of high-risk persons in the population has increased, previously idiopathic syndromes have been linked to foodborne infection, and as the nature and sources of the foods we eat has changed. Since the 1990s, some infections have been reduced by intensive and focused control efforts in some parts of the food chain, whereas others remain as common or are increasing.

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Some foodborne pathogens, like *Campylobacter,* Shiga toxin–producing *Escherichia coli* (STEC), nontyphoidal *Salmonella*, and *Listeria* have animal or environmental reservoirs, and humans are most often incidental hosts, after foods or ingredients are contaminated from those reservoirs somewhere along the chain of production, slaughter and processing. Secondary spread, particularly of *Salmonella* from food handlers and of STEC among young children can also be important. Other pathogens, like norovirus, hepatitis A, or *Shigella* have a primary human reservoir and cause foodborne illness when an infected human contaminates foods. Some of these pathogens also spread via water or animal contact, so the source of an infection is not necessarily food.

Our food supply is changing as more food is imported from distant lands, food processing becomes more centralized and industrial, and consumer tastes and cooking practices evolve. Food animals are raised in close quarters and are slaughtered and processed with ever-greater efficiency. Fresh fruits and vegetables are available year round, often shipped from warmer countries. Processed foods like peanut butter and raw cookie dough have caused large outbreaks when food safety measures were insufficient to prevent microbial contamination. In the kitchen, microwaving is replacing traditional cooking, which means that the heating that kills microbes is less thorough and more difficult to monitor. Consumers may desire local foods and foods eaten with minimal cooking as well as convenience. In 25 states, the sale of raw unpasteurized milk is now permitted, despite the raw milk–associated outbreaks that occur more frequently in those states.[1]

Diagnosing these infections is important for individual patients, who may be helped by specific treatment, and also for the general public health. Diagnosis and reporting is the foundation of public health surveillance, which makes it possible to detect and investigate outbreaks, to halt ongoing transmission, to better prevent similar outbreaks in the future, and to track progress in making the food supply safer.

PUBLIC HEALTH BURDEN OF FOODBORNE INFECTIONS

In 2011, the Centers for Disease Control and Prevention (CDC) estimated that each year approximately 48 million illnesses, 320 000 hospitalizations, and 3000 deaths caused by foodborne diseases occur in the United States.[2,3] The 31 known foodborne pathogens with sufficient data to make estimates account for an estimated 9.4 million illnesses, 56 000 hospitalizations, and 1400 deaths annually. These estimates are based on population surveys of acute gastroenteritis and pathogen-specific surveillance data. Eight pathogens account for most of the health burden caused by known pathogens (**Table 1**), accounting for 91% of illnesses, 88% of hospitalizations, and 88% of deaths. Norovirus accounts for most foodborne illnesses (58%), whereas nontyphoidal *Salmonella* accounts for the most hospitalizations (35%) and deaths (28%). Beyond the 31 defined pathogens, unspecified agents account for the balance of the total estimated burden. These unspecified agents represent those with insufficient data to estimate agent-specific burden (eg, *Plesiomonas* spp); known agents not yet identified as causing foodborne illness; marine and mycotic biotoxins; microbes, chemicals, or other substances known to be in food whose ability to cause illness is unproven or unknown; and agents yet to be identified.

The 2011 estimates update the previous 1999 estimate of 76 million cases with improved methods and data.[4] Because the analyses and data differed, direct comparison is not possible between the two sets of estimates. Additional population survey data used for the 2011 estimates revealed a more precise rate of acute gastroenteritis (0.6 per person per year) compared with data used for the 1999

Table 1
Reported incidence of culture-confirmed cases (from FoodNet in 2011) and estimated actual incidence of principal foodborne pathogens tracked in the United States

Pathogen	Culture-confirmed Cases per 100 000 Population	Estimated Actual Cases per 100 000 Population	Percent Foodborne (%)
Norovirus	n/a*	7000	26
Campylobacter spp	14.3	442	80
Salmonella	16.7	411	94
Cryptosporidium spp	2.8	408	8
Clostridium perfringens	n/a*	324	100
Shigella	3.2	165	31
STEC	2.1	88.7	77[a]
Staphylococcus aureus (foodborne)	n/a*	80.9	100
Yersinia enterocolitica	0.3	39	90
Toxoplasma gondii	n/a*	58	50
Vibrio	0.3	27	74[a]

* Surveillance data not available for all pathogens.
[a] Weighted mean for category.
Adapted from Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States–major pathogens. Emerg Infect Dis 2011;17(1):7–15; and CDC. FoodNet 2011, final report; 2012. Available at: http://www.cdc.gov/foodnet/PDFs/2011_annual_report_508c.pdf. Accessed January 28, 2013.

estimates (0.8 episodes per person per year), and new study data revealed a smaller proportion of norovirus illnesses to be foodborne (26%) compared with previous estimates (40%). The 2011 estimates also excluded travel- related illnesses associated with international travel and included uncertainty estimates (90% credibility limits).

NEW ANALYSES THAT ATTRIBUTE FOODBORNE ILLNESS TO SPECIFIC FOODS

The estimates of foodborne illnesses, hospitalizations, and deaths form the foundation for policy and research activities in foodborne diseases and food safety, akin to the US census data used for population-based policies and research. Because food safety policies and research are often focused on specific foods, analyses are needed that attribute foodborne illnesses to specific food commodities, called *foodborne illness source attribution*. These analyses can draw on a variety of data and can use several methods. The issue is challenging because most pathogens are transmitted through a variety of foods, the food source of individual illnesses is rarely known, and because there are so many types of foods. To help make attribution more systematic, the CDC proposed 17 categories of foods (or commodities), such as leafy greens, eggs, and shellfish, and suggested that *simple* foods could be defined as those whose major ingredients were a single commodity, whereas *complex* foods were those made with more than one commodity.[5]

One important source of data on food sources for a broad range of pathogens comes from outbreak investigations in which the source of illnesses is determined. Approximately 1000 foodborne outbreak investigations conducted at the local (ie, county or city), state, and national levels are reported each year to the CDC in the National Foodborne Outbreak Surveillance System.[6] Based on an analysis of illness in 1565 outbreaks that were linked to a single food commodity in 2003 to 2008, poultry,

leafy greens, beef, and dairy commodities were together responsible for more than half of the outbreak-associated illnesses (**Fig. 1**).

In 2013, a deeper analysis of outbreak data included outbreaks linked to complex foods (ie, foods that contain ingredients from more than one food commodity).[7] These foods have previously been excluded from such analyses. Using foodborne outbreak surveillance data from 1998 to 2008, the analysis included 4589 outbreaks with an implicated food vehicle and a single etiologic agent, accounting for 120 233 outbreak-associated illnesses caused by 37 agents. The percentage of outbreak-associated illnesses attributed to each of the 17 food commodities were applied to the pathogen-specific illnesses, hospitalizations, and deaths from the 2011 CDC estimates of public health burden to derive the annual disease burden by food commodity. Forty-six percent of the illnesses were attributed to the produce commodities, for which infections caused by norovirus were the major driver, and 29% of deaths were attributed to meat and poultry, largely caused by *Salmonella* and *Listeria* infections. This analysis combines information over 11 years into a single number and relies on the assumption that food vehicles for infection are similar for outbreak-related and sporadic cases. This assumption may be truer for some pathogens than for others, and it is important to remember that outbreak-associated cases account for only 3% of foodborne illnesses reported in active case-based surveillance.[8]

A different approach combined foodborne outbreak surveillance data from 1999 to 2008 with the opinions solicited from a panel of experts.[9] This analysis matched 14 major pathogens with 12 broad categories of foods resulting in 168 pathogen-food combinations and ranked them by quality-adjusted life-years (QALY) and cost of illness. The top 10 pairs accounted for more than $8 billion and 36 000 QALY (more than 50% of total). The top 5 were *Campylobacter* from poultry ($1257 million, 9541 QALY), *Toxoplasma gondii* from pork ($1219 million, 4495 QALY), *Listeria monocytogenes* in deli meats ($902 million, 3281 QALY), *Salmonella* from poultry ($693 million, 3513 QALY), and *L monocytogenes* from dairy products ($773 million, 2812 QALY). This analysis differs from the 2013 CDC report in that produce items are not included

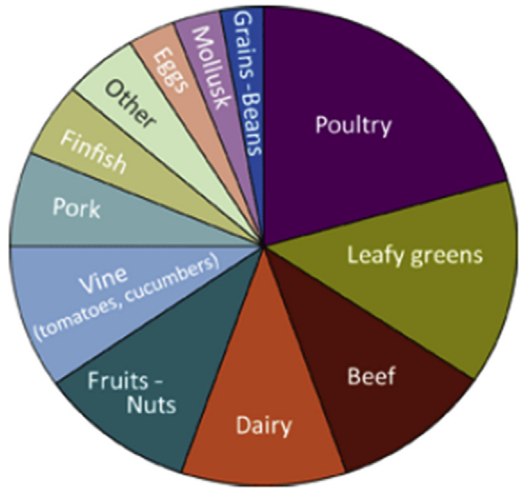

Fig. 1. Distribution of outbreak-associated illnesses in 1565 outbreaks caused by single food commodity and reported to CDC (2003–2008), National Foodborne Outbreak Surveillance System.

among the top 5 pathogen-commodity pairs, likely as a result of lower cost and QALY burden for illnesses caused by norovirus compared with the other pathogens and because complex food vehicles were not included in the analysis.

These estimates are being further refined using more methods and data sources in an interagency work group including the CDC, the Food and Drug Administration (FDA), and the US Department of Agriculture-Food Safety and Inspection Service (USDA-FSIS) called the *Interagency Food Safety Analytics Collaboration*.

RECENT SURVEILLANCE TRENDS

To reliably track some infections regularly transmitted through foods, the FoodNet active surveillance program was launched in 1996. FoodNet gathers systematic information on all laboratory-diagnosed infections with 8 different bacterial pathogens and 2 parasites often transmitted through foods, as well as hemolytic uremic syndrome (HUS), in 10 sites encompassing 15% of the US population.[10] In 2011, salmonellosis was the most common of the infections (16.4 cases per 100 000 population), followed by campylobacteriosis (14.3 per 100 000), shigellosis (3.2 per 100 000) and infection with Shiga toxin-producing *E coli* (2.1 per 100 000) (see **Table 1**). Diagnosed infections may represent only 1 in 20 to 1 in 30 of the actual infections.[2,8] Norovirus infection is the most frequent of all but is not captured in FoodNet because the clinical laboratory diagnosis of this infection is not routine at this time. FoodNet surveillance tracks changes in incidence for specific infections over time (**Fig. 2**). Compared with the baseline period from 1996 to 1998, infection with *Campylobacter, E coli* O157, *Listeria*, *Shigella*, and *Yersinia enterocolitica* have decreased significantly, although most of that occurred before 2003, with little recent progress. In fact, *Campylobacter* has increased slightly in the last 5 years. Importantly, *Salmonella* infections have not decreased over this 16-year span, although the incidence of individual serotypes has changed. The most common serotype, Typhimurium, declined significantly and the serotype Enteritidis first declined and then increased again (**Fig. 3**).

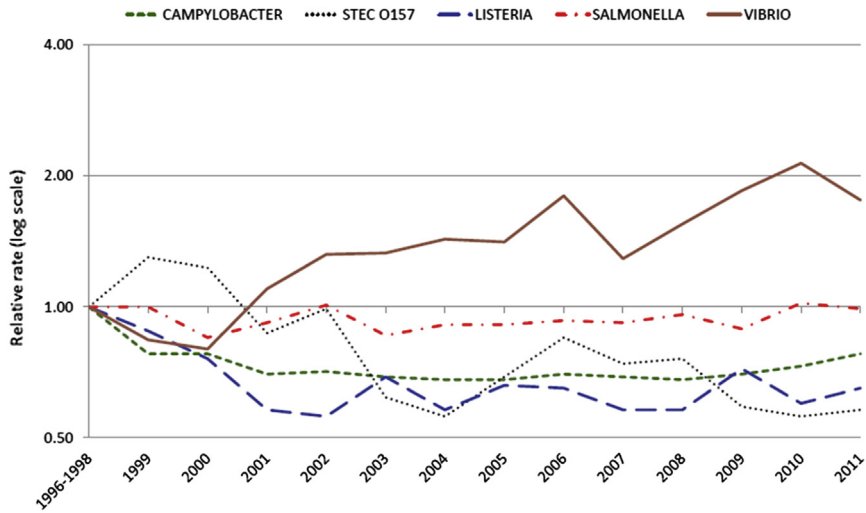

Fig. 2. FoodNet trends in relative incidence of 5 pathogens often transmitted by food from baseline in 1996–1998 to 2011 (http://www.cdc.gov/foodnet/data/trends/index.html).

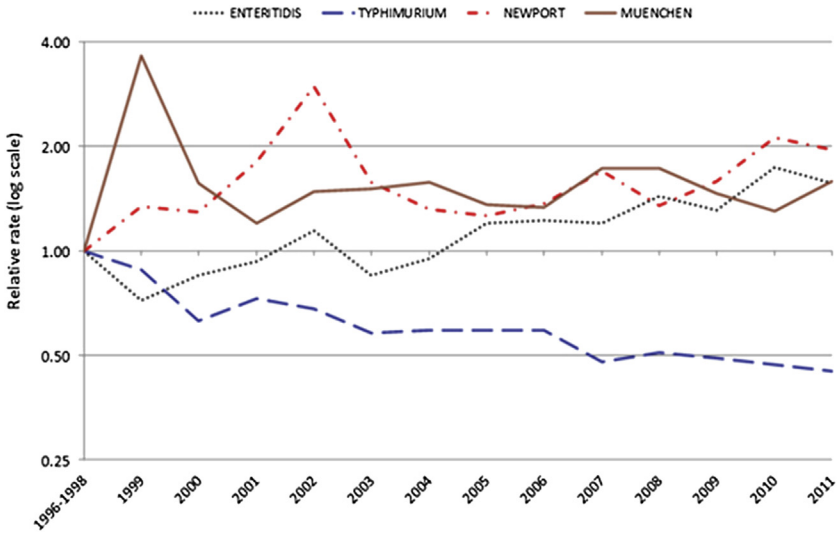

Fig. 3. FoodNet trends in top 4 serotypes of *Salmonella* from baseline in 1996–1998 to 2011 (http://www.cdc.gov/foodnet/data/trends/index.html).

Decreases in infections with *E coli* O157, *Listeria*, and *Campylobacter* likely reflect the impact of efforts by industry and regulatory authorities to address specific problems as well as a greater level of concern on the part of consumers. For example, changes in ground-beef processing and the designation of *E coli* O157 as an adulterant in ground beef by the USDA-FSIS (thus requiring immediate regulatory action if detected) were followed by a major decline in the frequency of contamination of ground beef with this organism by 2003.[11] More systematic and thorough cooking of ground beef in commercial and private kitchens also likely helped. The recent expansion of regulatory concern to the 6 other most frequent STEC in ground beef builds on this success.[12] The more recent appearance of outbreaks of STEC infection due to leafy greens, sprouts and other fresh produce shows that additional control measures are needed such as the produce regulations proposed by the FDA in 2013 to address the quality of agricultural water, wild animal incursions into produce fields and seed treatment of sprouts.[13] Beginning in the 1990s, voluntary efforts by the egg industry to reduce contamination with *Salmonella* Enteritidis and the growing use of pasteurized eggs were followed by decreases in the number of outbreaks and illnesses caused by *Salmonella* Enteritidis.[14,15] This success was incomplete; in 2010, eggs from 2 Iowa egg farms caused 1900 diagnosed infections in 47 states and led to the recall of half a billion eggs.[16] Coincidentally, a new regulation was published that same summer strengthening and making mandatory the previously voluntary industry program for egg farms, which may help prevent similar outbreaks in the future.[17]

The surveillance of foodborne outbreaks also reveals important trends. With improved diagnostic testing in public health laboratories, norovirus has emerged as the most frequent cause of foodborne outbreaks, typically from foods that are handled by infected kitchen workers.[18] Analysis of reported outbreaks shows that since the 1970s, fresh produce food vehicles account for a growing part of the overall problem. In the 1970s, fresh-produce food vehicles accounted for 1% of the outbreaks for

which a vehicle was determined and 1% of the illnesses associated with those outbreaks.[19] By the 1990s, these had increased to 6% of the outbreaks and 12% of the outbreak-associated illnesses. The importance of produce as a source of outbreaks has continued to increase. In 2009 to 2010, 10% of the outbreaks with a known food vehicle and 14% of the outbreak-associated illnesses were attributed to one of several produce categories.[6] The 2013 CDC attribution analysis that included the complex food vehicles estimated that 46% of foodborne illnesses were related to produce.[7] Some produce outbreaks may reflect a specific biologic association that *Salmonella*, *E coli* O157:H7, and other pathogens have with plants.[20] Recent observations of microbial adaptations that facilitate internalization and persistence inside plant hosts suggest that for some bacteria, colonizing a plant may be a strategy for reaching the next herbivorous host.

Progress in food safety proceeds in a cycle linking surveillance, investigation, and prevention. As recurrent problems are identified by repeated outbreaks or careful monitoring, specific points of intervention are identified and targeted measures applied. If prevention is improved by those measures, the incidence of illness decreases. For example, a series of outbreaks linked to raw fruit juice and cider in the 1990s led to new requirements for pasteurizing juices, and such outbreaks are now less frequent.[21] When surveillance improves, such as when pathogen subtyping is introduced routinely, more outbreaks are detected. Prevention can improve further by showing which infections are caused by precisely the same pathogen subtype and, thus, may have the same source; subtyping can find clusters of related cases that would otherwise be unapparent. Thus, improved subtype–based surveillance can have the seemingly paradoxic effect of both increasing the number of outbreaks detected and decreasing the incidence of disease. For example, outbreaks of listeriosis used to be rarely detected in the United States. Then in 1996, PulseNet subtyping of *Listeria* began nationwide, which increased the number of outbreaks detected by an order of magnitude, including large multistate foodborne outbreaks (**Fig. 4**). Many of those outbreaks were caused by processed meats, like hot dogs and sliced deli turkey. Changes in the processed-meat industry and its regulation made contamination with *Listeria* less likely, and listeriostatic compounds added to many meat

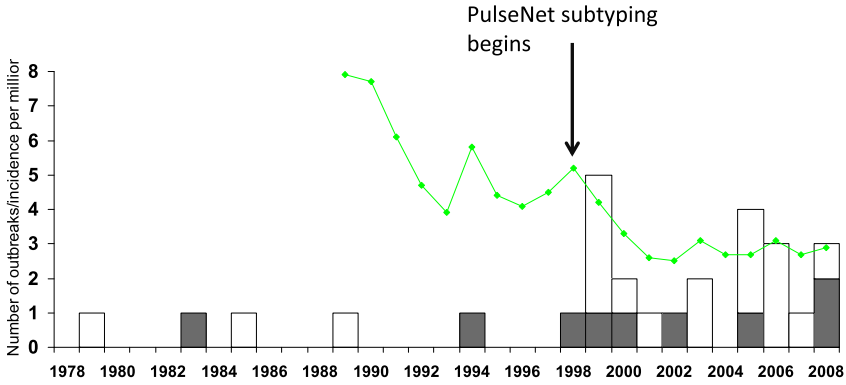

Fig. 4. Incidence of *Listeria* infections per million and outbreaks of listeriosis (1978–2008). White bars indicate single-state outbreaks, gray bars indicate multistate outbreaks, and solid line indicates incidence. (*Data from* Cartwright EJ, Jackson KA, Johnson SD, et al. Listeriosis outbreaks and associated food vehicles, United States, 1998–2008. Emerg Infect Dis 2013;19(1):1–9.)

products now inhibit *Listeria* growth even if contamination occurs. Outbreaks from processed meats became less frequent, and the incidence of listeriosis declined.[22]

TRENDS IN ANTIMICROBIAL RESISTANCE

Antimicrobial resistance can complicate clinical treatment and can also increase the number of illnesses that occur because resistant strains may cause illness at lower doses when the exposed person is also taking an antibiotic to which the organism is resistant.[23] Antimicrobial resistance in clinical isolates of enteric bacteria has been tracked systematically at the CDC since 1996 for *Salmonella* and 1997 for *Campylobacter*. In the late 1990s, multidrug-resistant strains of *Salmonella* Typhimurium and of *Salmonella* Newport emerged and spread.[24] Multidrug-resistant Typhimurium and Newport strains continue to circulate at lower frequencies, and the plasmid that encoded the Newport resistance has moved into other *Salmonella* serotypes. Currently 11% of clinical nontyphoidal *Salmonella* infections are caused by multidrug-resistant strains, that is, by strains resistant to 2 or more classes of agents, substantially lower than in the 1990s (**Fig. 5**).[25] Strains of serotype Heidelberg that are resistant to ceftriaxone have recently emerged; in 2010, 24% of Heidelberg strains were resistant.[25] Fluoroquinolone resistance in *Campylobacter* from humans increased rapidly after this class of drug was approved for use in poultry. Fluoroquinolone-resistant campylobacter infections were related to eating poultry in the United States and to international travel.[26] In 2005, the FDA withdrew approval to use fluoroquinolones in poultry. Fluoroquinolone resistance in isolates from humans peaked at 25.8% of *Campylobacter jejuni* strains in 2007, declining to 21.8% as of 2010 (see **Fig. 5**). Macrolide resistance in *Campylobacter* remains rare.

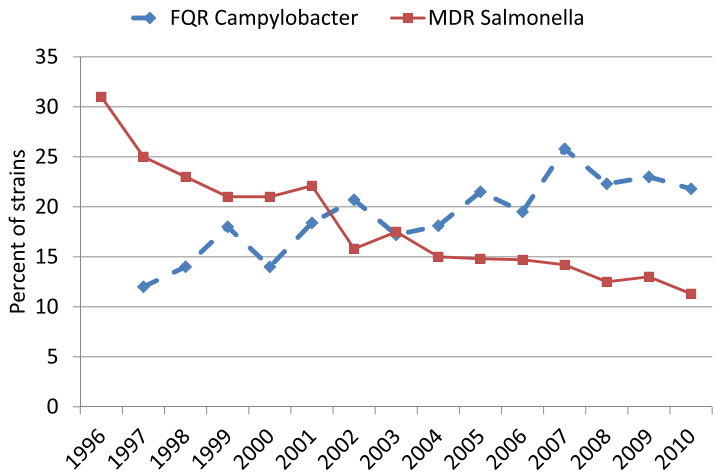

Fig. 5. Proportion of *Salmonella* resistant to 2 of more antimicrobial agents and of *Campylobacter jejuni* resistant to fluoroquinolones from 1996–1997 to 2010, National Antimicrobial Resistance Monitoring System for isolates from humans. FQR, Fluoroquinolone resistant; MDR, multidrug resistant. (*Data from* CDC. National Antimicrobial Resistance Monitoring System for Enteric Bacteria - annual report for 2000. Available at: http://www.cdc.gov/ncidod/dbmd/narms/. Accessed January 31, 2013; and CDC. National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): human isolates final report, 2010. In: Centers for Disease Control and Prevention. Atlanta (GA): 2011. Available at: http://www.cdc.gov/narms/pdf/2010-annual-report-narms.pdf. Accessed January 31, 2013.)

THE SIGNIFICANCE OF MULTISTATE FOODBORNE OUTBREAKS

Most foodborne outbreaks occur at the county level and have local solutions. Of the almost 5000 foodborne outbreaks that were reported from 2006 to 2010, 94% were confined to a single county (CDC, 2012, unpublished data). Typically these local outbreaks are investigated by local public health officials who identify specific food preparation and handling problems, leading to corrections to food handling in retail, institutional, or catering kitchens.

Two percent of the approximately 5000 reported outbreaks involved patients who were exposed in multiple states. These multistate outbreaks accounted for 7% of all outbreak-associated illnesses, 31% of hospitalizations, and 34% of deaths. Thus, multistate foodborne outbreaks tend to be larger and more severe than local outbreaks. Investigating multistate outbreaks typically requires national coordination, and they often garner national press attention. Multistate outbreaks are the result of food contamination occurring during production, slaughter, processing, or distribution of foods that are widely distributed before the foods reach the kitchen. These investigations often reveal important gaps in food safety regulation and industry processes, with major implications for food safety policy in government and industry.

Outbreak investigations can be complicated if the contaminated food is an ingredient in multiple other foods (eg, spices) or is a minor component of dishes that is not likely to be remembered, (eg, sprouts). Therefore, thorough public health investigations are critical to stop the outbreak by removing contaminated food from the marketplace and also to prevent similar ones from occurring in the future. Multistate outbreaks serve to identify new and previously unknown risks that develop as the nation's food production and supply systems continuously change. Two recent examples illustrate this impact.

MULTIDRUG-RESISTANT *SALMONELLA* AND GROUND TURKEY

In May of 2011, the CDC detected a cluster of illnesses caused by a particular strain of *Salmonella* serotype Heidelberg infections; the outbreak strain was resistant to multiple antimicrobial agents, including ampicillin, streptomycin, tetracycline, and gentamicin. A total of 136 cases from 34 states were eventually associated with the outbreak.[27] Multiple lines of investigative evidence implicated ground turkey as the food vehicle. Most ill people reported ground turkey consumption. The outbreak strain of *Salmonella* Heidelberg was isolated from ground turkey remaining in a patient's home and from 5 ground-turkey samples purchased at retail stores, and source tracing of the ground turkey consumed by patients from retail store purchase sites led to a single large turkey-processing facility. As a result, the implicated company recalled approximately 36 million pounds of ground-turkey products that may have been contaminated with the multidrug-resistant strain of *Salmonella* Heidelberg. This large and severe outbreak led to the recall of a raw poultry product caused by contamination with *Salmonella*. The company has implemented additional measures to reduce the prevalence of *Salmonella* among its source turkey flocks and turkey-meat products, reducing the risk of future illnesses and outbreaks. That same spring, the USDA-FSIS finalized tighter standards for permissible levels of *Salmonella* in raw poultry.[28]

SALMONELLA AND PEANUT BUTTER

Thirteen cases in 12 states detected by national molecular subtype surveillance heralded an historic outbreak of *Salmonella* serotype Typhimurium infections in November 2008, linked to peanut butter and peanut paste that was used as an

ingredient in thousands of food products.[29] More than 700 cases were eventually reported from 46 states, although many more were likely affected but not captured by national public health surveillance systems; 9 case-patients died. This outbreak exemplified the difficult epidemiologic task of implicating contaminated ingredients used in multiple foods. Many of the early illnesses were related to an institutional peanut butter rather than peanut butter available in retail stores. The connection with peanut butter was only identified because of an investigator's suspicion that the same food might be served at different institutions with cases (including schools and nursing homes). Then, even after that peanut butter was recalled, persons with no institutional connections continued to become ill, and it was learned that the same peanut butter factory also provided peanut paste to other companies to make a range of peanut butter–flavored foods from peanut butter crackers to dog biscuits. The resulting recall of peanut-containing products was one of the largest in the United States; more than 2100 different products from more than 200 companies were recalled.

This outbreak was the second largest outbreak of salmonellosis from peanut butter in the United States, following closely after the first one that occurred in 2006.[30] Before these outbreaks, low water activity foods, such as peanut butter, were not considered foods at risk for significant *Salmonella* contamination. That perception has changed as a result of these large outbreaks, and the need for specific food safety measures for such foods is now evident.[31] These outbreaks helped to propel the development of new legislation in 2011, the Food Safety Modernization Act, which is changing the approach to regulation and oversight of many parts of the food industry.[32]

CRITICAL ROLE OF PATHOGEN SUBTYPING

Traditional case surveillance activities, and citizen reports of illnesses, often serve to identify local foodborne outbreaks when illnesses are clustered within a community over a short period of time. However, national scale outbreaks caused by widely distributed foods often cannot be recognized early in their onset by local clustering of cases. In these circumstances, only one or a few cases may occur in any one state, defying identification by traditional surveillance, unless they become extremely large. In most circumstances, national-scale outbreaks would not be detected at all.

For this reason, surveillance based on subtyping the pathogens from patients in public health laboratories has been established for several foodborne pathogens. Subtype-based surveillance started with *Salmonella* serotyping, which has been done in state and large city health department laboratories in all 50 states since 1967.[33] Serotyping all *Salmonella* isolates provided a new means of finding dispersed outbreaks, which has been central to *Salmonella* surveillance ever since. Starting in 1996, the PulseNet molecular subtyping system has provided enhanced strain discrimination for surveillance.[34] PulseNet is a national network coordinated by the CDC that links 87 public health and food regulatory laboratories, including all state health department laboratories, some large city health department laboratories, and laboratories at the CDC, USDA, and FDA. PulseNet-participating laboratories perform routine molecular subtyping of bacterial foodborne pathogens including *Salmonella*, STEC, *Listeria*, and *Shigella*. State health departments require or request clinical laboratories to send in isolates of these pathogens to serotype *Salmonella* and *E coli* and to conduct molecular analyses. The principle method of molecular analysis is pulsed-field gel electrophoresis, although other complementary methods, such as multivariable tandem repeat analysis, may also be used. The subtype data are submitted to a national database at the CDC in real time, and the data are reviewed to identify clusters of molecular subtypes that may represent outbreaks. The overarching

presumption is that persons infected with the same genetic strain of a pathogen likely acquired their infection from the same source. PulseNet now gathers approximately 50 000 patient isolate subtype submissions each year (**Fig. 6**). Each participating laboratory can view the data, and local and state health departments regularly use PulseNet to help detect clusters and define cases for investigation at their level. Approximately 200 multistate clusters are assessed epidemiologically each year leading to 15 to 20 large multistate outbreak investigations, most of which would not be detected without PulseNet. PulseNet does not replace traditional epidemiologic investigation but rather enhances it, focusing detailed interviews on those patients most likely to have an exposure in common and assessing the similarity of isolates from food or other sources to those from patients. The success of the PulseNet system is being replicated for other pathogens, including molecular subtype surveillance for norovirus, *Cryptosporidium*, and *Mycobacterium tuberculosis*.

LOOKING FORWARD

New Culture-Independent Diagnostic Tests

New diagnostic tests for enteric infections that do not depend on bacterial culture and isolation are changing the landscape of foodborne disease diagnosis and outbreak detection. These culture-independent diagnostic tests are 2-edged tools. A positive consequence is that diagnosis can be improved. For example, tests that detect Shiga toxin make it simpler to find infections with non-O157 STEC, and new *Campylobacter* diagnostic assays based on enzyme immunoassay make it possible to more rapidly start treatment. Public health surveillance currently depends on definitive identification by culture and on characterizing bacterial isolates by serotype, subtype, and resistance pattern. If new tests are more likely to yield a positive signal or are used more broadly than current diagnostics, the number of reported cases could increase because of the change in diagnostic testing rather than because the actual frequency of infection has increased.[35] Most importantly, unless bacterial isolates are still available for characterization in public health laboratories, the ability to detect widespread outbreaks will disappear, returning us to the limited capacity of the 1960s whereby clusters of related infections disappear into the background incidence of infections.[36] Thus, the CDC has recommended that when a specimen has evidence of Shiga toxin

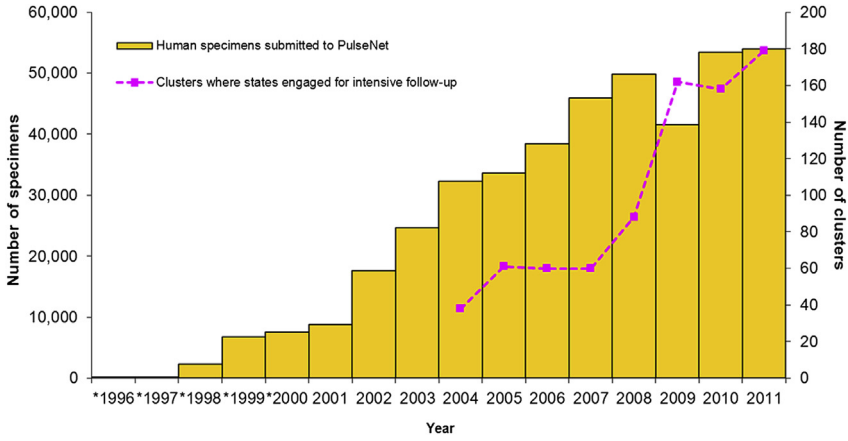

Fig. 6. Number of isolates from humans uploaded to PulseNet and clusters with intensive epidemiologic follow-up by year, 1996 to 2011 (CDC, 2012, unpublished data). *Data are incomplete for 1996 to 2000.

by a rapid test, it is important to culture that specimen for STEC, either in the clinical laboratory or by sending the positive broth to the state public health laboratory for culture there.[37,38] Similarly, if rapid *Salmonella* diagnostics are used, reflex bacterial culture of positive specimens will be critically important to preserve the ability to detect and investigate outbreaks, at least for the near term. In the future, new diagnostic surveillance platforms based on DNA sequencing that include specific gene markers for serotype, molecular subtype, virulence markers, and antimicrobial resistance could offer even better detection and characterization capacity than currently exists, but these methods urgently need to be developed. Public health laboratory-based surveillance of the future may be based on rapid transfer of selected DNA sequences to public health databases rather than referral of the actual strain itself.

New Pathogens and New Food Vehicles

New or unusual pathogens are identified, usually in the course of investigating outbreaks, and new food hazards can be characterized. In 2011, an outbreak of sprout-associated illnesses in Germany drew attention to a highly pathogenic combination of virulence factors in *E coli* rarely seen before, a strain of *E coli* O104:H4 that was both enteroaggregative and Shiga toxin producing.[39,40] In Germany, 3816 cases were reported, 22% (845) of which developed HUS and 54 died, whereas a related outbreak occurred in France a month later.[41] The remarkably severe illness may have been caused by the combination of adherence factors and Shiga toxin 2a, a particularly virulent toxin subtype. In 2008, an outbreak of gastroenteritis associated with consumption of chicken following a wedding reception in Wisconsin seems to have been caused by *Arcobacter butzleri,* a pathogen similar to *Campylobacter* that is also frequently found on poultry.[42] This outbreak is the first foodborne outbreak to be identified with this pathogen, which is difficult to isolate with traditional microbiological approaches but can be detected through gene probes. The calicivirus Sapovirus is emerging as the likely cause of oyster-associated foodborne outbreaks in Japan.[43]

New and unsuspected food vehicles are also identified in these investigations. Since 2006, at least 15 foods have been the source of outbreaks that had not previously been recognized as problems in the United States (**Box 1**). Of these 15, 11 (73%) were derived from plants and 7 (14%) were imported. Each of these represents a new challenge to food safety authorities. *Listeria* outbreaks have recently been associated with fresh produce items like sprouts, celery, and cantaloupes, which were not previously recognized as major hazards for that pathogen.[22] Outbreaks traced to imported foods, including produce, spices like pepper, and scraped tuna, have recently been associated with major outbreaks of *Salmonella* infection, highlighting the ease with which pathogens can be disseminated around the world through trade and travel (See www.cdc.gov/salmonella/outreaks.html).

In other parts of the world, important foodborne-disease challenges have emerged in the last decade. In South America, Chagas disease is emerging as a foodborne infection even as traditional vector-borne Chagas wanes. Outbreaks have been linked to fresh unpasteurized acai juice and to fresh guava juice.[44,45] Infected triatomid insects present in the fruits as they are processed may be the source of contamination. Fortunately, pasteurization of juice eliminates trypanosomes, so the risk is limited to consumption of fresh unpasteurized juice. In Western China, foodborne cholera outbreaks caused by toxigenic *Vibrio cholerae* O139 have followed banquets at which steamed soft-shelled crabs were served.[46,47] *Vibrio* has also been found in crabs at retail locations and may be present in the waters where the crabs are raised to meet the banquet market.[48] In Taiwan, multidrug-resistant *Salmonella* Choleraesuis infections, often presenting as aortitis, have been difficult to treat and have been

Box 1
Fifteen new food vehicles identified in outbreaks affecting the United States since 2006 (CDC unpublished data)

- Bagged spinach
- Carrot juice
- Peanut butter
- Broccoli powder on a snack food
- Dry dog food
- Frozen potpies
- Canned chili sauce
- Hot peppers
- White and black pepper
- Raw cookie dough (likely the flour)
- Hazelnuts
- Fenugreek sprouts
- Papayas
- Pine nuts
- Raw scraped tuna

resistant to fluoroquinolones and more recently to ceftriaxone.[49,50] It has been suggested that this is a consequence of a simultaneous epizootic of these infections in pigs and that at least some of this resistance is a consequence of the use of antimicrobials to treat pigs.[51] In Bangladesh, outbreaks of lethal Nipah virus encephalitis have been linked to drinking sugar palm sap, a sweet beverage like maple sap that is harvested from trees in pots overnight.[52] Giant fruit bats harbor the Nipah virus without signs and shed it in their urine. The palm sap becomes contaminated when fruit bats visit the trees to harvest sap from pots themselves. In some outbreaks, respiratory symptoms and limited person-to person transmission has occurred, a scenario that was amplified and dramatized in the 2011 movie *Contagion*.

More syndromes may prove to be foodborne in the future, just as HUS has been linked to STEC infection and Guillain-Barre syndrome to *Campylobacter* infection. It has been suggested that urinary *E coli* infections may follow transient gut colonization with uropathogenic strains after food exposure.[53,54] There is growing evidence that irritable bowel syndrome may be associated with *Campylobacter* and other enteric infections.[55] *Toxoplasma gondii* is known to induce important behavior changes in the mice they infect, making them curious about cats rather than fearful and, thus, more likely to be caught and eaten, perpetuating the predator-prey cycle to the benefit of the parasite.[56] Many humans have long-term infection with *Toxoplasma*, as a result of foodborne exposures and contact with kittens.[57] It has been suggested that the presence of encysted *Toxoplasma* encysted in human brains may also have neuropsychiatric consequences.[58] Other hypotheses link illness to the state of the gut flora considered as a community, which is modulated by the microbes and nutrients in food. This rapidly evolving arena includes the demonstration that in mice, the efficiency of energy extraction from foods is affected by gut flora, thereby perhaps affecting obesity.[59] It also includes the hygiene hypothesis that suggests the immune system is more likely to react to autogenous antigens because of

reduced exposure to antigenic diversity in childhood.[60] The health benefit of consuming specific probiotic organisms or beneficial communities of organisms is a target for further research.

Critical Role of the Specialist in Infectious Diseases

Public health surveillance and outbreak detection for foodborne diseases depends to a great degree on the actions of astute clinicians. Knowledge of the clinical syndromes of foodborne diseases guides appropriate diagnostic testing to identify significant pathogens and the treatment of infections. In many instances, the standard stool culture panel available at the local clinical laboratory is either unnecessary (eg, for illness very likely caused by norovirus infection) or insufficient (eg, for illness consistent with STEC infection or *Vibrio*). Some of the new nonculture diagnostic tests currently or soon to be available can have variable sensitivity or specificity and may require culture to confirm and characterize the pathogen to guide treatment (ie, Shiga toxin profile, antimicrobial sensitivity testing). Appropriate testing also serves the public's health through national surveillance systems, and a cultured isolate may also be critical to linking ill patients involved in an outbreak.

Infectious diseases physicians should develop relationships with local public health officials to share information about patients or groups of patients with illnesses, which may portend a public health issue requiring public health investigation and intervention. Infectious diseases specialists have a critical role to play within their professional communities to guide and teach primary care and other providers of the importance of appropriate testing and diagnosis of patients with significant foodborne illness and to provide direct communication with public health officials.

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