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Traced to Pasteurized Milk***

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Massive Outbreak of Antimicrobial-Resistant Salmonellosis Traced to Pasteurized Milk

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Two waves of antimicrobial-resistant *Salmonella typhimurium* infections in Illinois totaling over 16 000 culture-confirmed cases were traced to two brands of pasteurized 2% milk produced by a single dairy plant. Salmonellosis was associated with taking antimicrobials before onset of illness. Two surveys to determine the number of persons who were actually affected yielded estimates of 168 791 and 197 581 persons, making this the largest outbreak of salmonellosis ever identified in the United States. The epidemic strain was easily identified because it had a rare antimicrobial resistance pattern and a highly unusual plasmid profile; study of stored isolates showed it had caused clusters of salmonellosis during the previous ten months that may have been related to the same plant, suggesting that the strain had persisted in the plant and repeatedly contaminated milk after pasteurization.

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IN MARCH 1985, state and federal health agencies began an investigation that ultimately showed that multiple production dates of 2% low-fat milk from a northern Illinois dairy processing plant caused the largest outbreak of salmonellosis ever recorded in the United States. The implicated plant was one of the largest in the Midwest; it processed approximately 1.5 million pounds of raw milk from southern Wisconsin and northern Illinois cooperatives daily and delivered most of it to stores of one large retail chain. The plant's products were suspected to have

caused an August 1984 outbreak of approximately 200 cases of salmonellosis in northern Illinois, but the results of that investigation were not considered conclusive.

The *Salmonella typhimurium* strain that caused the August outbreak had an unusual antimicrobial-resistance pattern. On March 28, 1985, an infection-control nurse reported isolation of *S typhimurium* strains with the unusual antimicrobial-resistance pattern that she had last noted during the August 1984 outbreak. On the next day, 31 similar infections were reported, and the investigation was started. This report presents the epidemiologic and laboratory studies that led to the identification of pasteurized milk as the vehicle of transmission, examines the risk factors associated with symptomatic infection, describes the emergence of the unusual epidemic strain, and discusses how the milk may have become contaminated.

SUBJECTS AND METHODS Epidemiologic Investigations

Case Finding.—A case was defined as nausea, abdominal pain, or diarrhea (three or more loose bowel movements in a 24-hour period) in an Illinois resident with a stool culture that yielded *Salmonella* group B, reported to the Illinois Department of Public Health (IDPH) after March 29, 1985. Cases were ascertained through infection-control nurses at local hospitals and through microbiology laboratories. Patients or their parents/guardians were interviewed by telephone regarding symptoms, hospitalization, and exposures. From our initial case interviews, we suspected several food items, including milk, as the source.

Case-Control Studies.—Two case-control studies were conducted to identify vehicles of transmission. Study 1 was restricted to salmonellosis cases reported between March 30 and April 1, 1985 (implicated milk product A). Study 2 was conducted one week later after ongoing case interviews suggested that a second milk product (product B) might be contaminated. In study 2, cases were restricted to persons who were described on April 8, 1985, as having stool cultures that yielded *Salmonella* group B. In both studies, age- and neighborhood-matched control subjects were contacted using telephone directories organized by street rather than by name. We asked patients and control subjects about multiple food and environmental exposures, including the brand(s) of milk consumed in the two weeks before the onset of the patient's

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illness, and then about consumption of products A and B. There had been no publicity about milk being a suspected source during study 1; during study 2, the public knew only of the association with product A.

A third case-control study examined potential risk factors for development of salmonellosis. Patients infected with the outbreak strain were compared with age- and neighborhood-matched well controls for multiple potential risk factors (use of antimicrobials, antacids, cimetidine hydrochloride, or immunosuppressant drugs and previous gastric surgery). We also collected and analyzed data about illness and milk consumption among family members of the patients.

Surveys of Illinois Counties.—To estimate the total number of *Salmonella* infections in the community, we surveyed randomly selected households in two northern Illinois counties by telephone. Heads of households or family members aged 16 years or older were asked about symptoms and milk-drinking habits for each household member and family milk-buying habits for the previous month. We defined a milk-related salmonellosislike illness as a diarrheal illness that lasted at least 24 hours in someone who had consumed products A or B since March 21, 1985.

Interviews Regarding Culture-Confirmed Cases.—State and local health departments interviewed 15 459 (93%) of the 16 659 patients with culture-confirmed cases using questionnaires that asked about exposures, symptoms, household contacts, treatment, and hospitalization and about milk consumption and antimicrobial use in the month before onset of symptoms.

Laboratory Investigations

Three laboratory studies were conducted. First, we investigated the distribution of the epidemic strain of *Salmonella* in the United States by evaluating (1) 369 human isolates of *S typhimurium* from two nationwide studies of *Salmonella* since 1979, (2) representative isolates from 14 outbreaks that had occurred since 1969, and (3) 32 animal isolates of *S typhimurium* collected by the US Department of Agriculture. Second, we evaluated 574 isolates of *S typhimurium* from sporadic cases of salmonellosis in Wisconsin residents between January 1984 and March 1985 to see if the strain was previously present in the state where most of the milk originated. Third, we examined 486 isolates of *S typhimurium* from sporadic cases of salmonellosis in Illinois residents between January 1984 and March 1985

(excluding the outbreak period in August 1984) to determine when this unusual strain emerged in Illinois. We attempted to identify the original source of this unusual strain by reviewing questionnaires completed routinely by local health departments for salmonellosis cases; we compared persons infected with the outbreak-related strain of *S typhimurium* with a control group of persons infected with *S typhimurium* sensitive to all antimicrobials.

Clinical isolates were sent to the Illinois State Laboratory for serotyping and to the Centers for Disease Control (CDC), Atlanta, for serotyping, antibiogram confirmation, and plasmid analysis. At the CDC, all *Salmonella* isolates were screened by replica plating for the outbreak antimicrobial-resistance pattern; the results were confirmed for selected isolates with Kirby-Bauer disks.^{1,2} The plasmid DNA from *S typhimurium* isolates that were resistant to ampicillin, carbenicillin, tetracycline, streptomycin, and sulfisoxazole was analyzed by a modified Birnboim and Doly technique,³ and compared by agarose gel electrophoresis.⁴ The identity of plasmids was confirmed by electrophoresis of DNA fragments generated by restriction enzyme digestion with *Hind III*. Outbreak strains were identified by their characteristic antimicrobial susceptibilities and plasmid profiles.

Dairy Processing Plant Investigation

Illinois assembled a task force of representatives from federal and state governments, industry, and a university. They reviewed dairy plant records, examined the plant, consulted the plant designer, and conducted specialized tests. To search for the source of the outbreak strain, 505 samples of pooled raw milk were collected between April 23 and June 14, 1985; these samples represented milk from 2786 individual producers in northern Illinois and southern Wisconsin that could have supplied milk on the three implicated production days. Multiple samples of milk products produced at the processing plant between March 30 and April 9, 1985, other nonfluid milk products, and swabs from the plant environment were analyzed by the IDPH, a private laboratory, the Food and Drug Administration, and the CDC.

RESULTS

Epidemiologic Results

Case-Control Studies.—The first case-control study, with 32 case-control pairs, showed that illness was associated with drinking brand A 2% milk that was dated with a March 29, 1985, expiration date ($P < .001$, two-tailed bino-

mial test; odds ratio [OR] > 5.19). Since the expiration date was always nine days after pasteurization, the milk was produced on March 20. On the day the results were obtained (April 1, 1985), a press conference advised consumers to discard brand A 2% milk that was dated March 29. *Salmonella typhimurium* was later isolated from an unopened carton of brand A 2% milk that was dated March 29. On April 8, local health departments noted that some of the most recent cases occurred in persons who had drunk a different milk from the same plant, brand B 2% milk that was dated April 8. On April 9, an unopened carton of brand B 2% milk that was dated April 8 had a preliminary report of cultures positive for *Salmonella*. At that time, the second case-control study had 13 case-control pairs and showed that the most recent cases of *Salmonella* group B infections were associated with brand B 2% milk that was dated April 8 ($P = .001$, two-tailed binomial test; OR > 1.92). On the next day, the dairy was closed, and all of its milk products were recalled.

Most illnesses occurred in two clusters that peaked on March 29 and April 7, 1985 (Fig 1). Most patients in the first cluster drank brand A 2% milk that was dated March 29, while most patients in the second cluster drank brand B 2% milk that was dated April 8. The geographic distribution of cases was similar to the distribution of the implicated lots of milk. Cases were distributed mainly in northern Illinois, with the communities surrounding Chicago being the most severely affected (three reported cases per 1000 residents).

The third case-control study evaluated risk factors associated with illness in 50 case-control pairs. *Salmonella* group B gastroenteritis was associated with use in the month before illness of antimicrobials to which the organism was resistant ($P = .003$, two-tailed binomial test; OR = 5.5; 95% confidence interval, 1.22 to 24.81), but not with use of antacids, cimetidine, or immunosuppressant drugs, nor with a history of gastric surgery. Among family members who drank the suspect milk, ill persons were more likely than well persons to have used an antimicrobial to which the organism was resistant in the month before onset of illness ($P < .035$, t test for clustered samples). In this study, there were no cases, controls, or case family members who had taken an antimicrobial to which the organism was sensitive. Antimicrobials lowered the dose of *Salmonella* needed to cause disease; the usual number of cups of milk drunk was less for ill

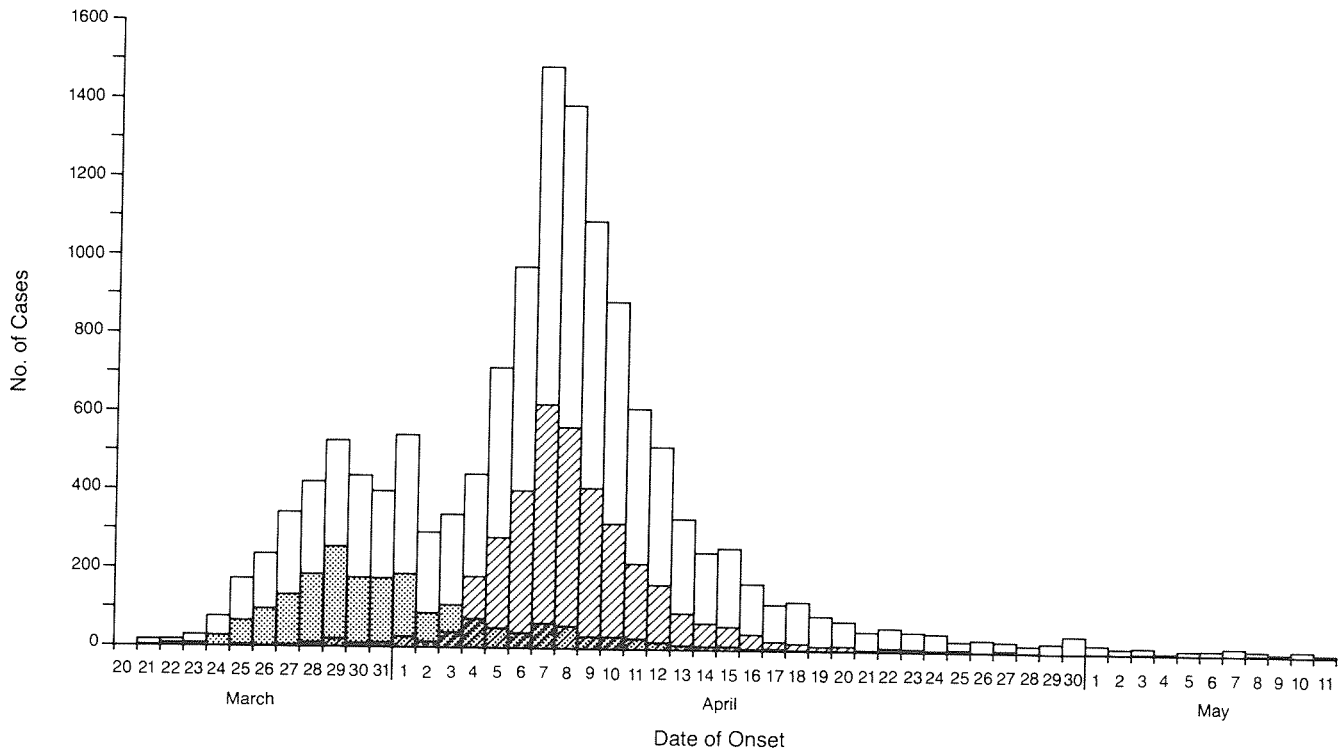


Fig 1.—Cases of *Salmonella typhimurium* gastroenteritis by date of onset and product consumed, Illinois, March 21 to May 10, 1985. Dotted bars indicate brand A 2% milk (3/29); hatched bars, brand B 2% milk (4/8); and open bars, unknown or other expiration dates of brands A and B and other brands.

Table 1.—Relationship Between Use of Antimicrobials in Month Before Illness and Average Daily Consumption of Implicated Brands of Milk*

	Took No Antibiotics		Took "Resistant"† Antibiotics		P‡
	Cups	No.	Cups	No.	
Ill	3.6	38	2.4	16	.010
Well	1.9	76	1.6	5	.184
P‡	.000039		.034		...

*By case and case family members (case-control study 3). No. indicates number of subjects in the cell.

†Resistant antibiotics are antibiotics to which the outbreak strain of *Salmonella typhimurium* was resistant.

‡By t test for clustered samples.

persons who had taken antimicrobials in the month before illness than for ill persons who had not taken antimicrobials (2.4 vs 3.6 cups, $P = .01$, t test for clustered samples) (Table 1).

Surveys of Illinois Counties.—The two telephone surveys showed that approximately 30% of households surveyed recalled drinking the implicated brands of 2% milk during the study period; approximately 6.5% of persons in the surveyed households were identified as cases of salmonellosis (Table 2). Sixty-nine percent of those people identified as having a salmonellosislike illness recalled drinking brand A or B

Table 2.—Telephone Surveys of Salmonellosislike Illness in Two Representative Illinois Counties to Estimate Number of Persons Affected in Illinois

	Survey	
	1	2
No. of households (No. of people) included	256 (777)	230 (730)
No. of salmonellosislike illnesses identified	45	53
No. of ill persons recalling drinking brand A or B 2% milk in month before illness	31	39
No. of households using brand A or B 2% milk during study period*	59	88
No. of households using brand A or B 2% milk with at least 1 illness in household	13	20
Estimate of total No. of Illinois residents with outbreak-related <i>Salmonella</i> gastroenteritis†		
Unadjusted	255 209	270 830
Adjusted for background diarrhea‡	197 581	168 791

*April 14 to 25, 1985.

†Calculation of estimate of unadjusted number of illnesses in Illinois caused by the implicated milk (IM):

(1) No. Illnesses Associated With IM in Survey County = (No. Ill in Sample Who Drank IM/No. in Sample) × Population of Survey County

(2) No. Illnesses Associated With IM in Illinois = (Gallons of IM Distributed in Illinois/Gallons of IM Distributed in Survey County) × No. Illnesses Associated With IM in Survey County

‡Background assumes that persons with salmonellosislike illnesses in the surveys but no recollection of drinking brand A or B 2% milk during the month before onset represent "background" diarrhea unrelated to the milk.

2% milk in the month before illness. Among drinkers of brands A and B 2% milk, children less than 10 years of age had the highest attack rate (Table 3). Using the distribution of implicated milk and the amount of illness in the survey samples, our estimates from the two surveys for the number of persons

affected in Illinois during this March and April 1985 outbreak were 168 791 and 197 581 persons (Table 2).

Questionnaires.—Analysis of questionnaires administered to 15 459 patients with culture-confirmed cases showed that sexes were affected equally. Children 1 to 4 years of age were most

Table 3.—Age-Specific Attack Rate of Salmonellosislike Illness in Persons Who Drank Milk Products A or B After March 21, 1985, in Surveys of Two Illinois Counties, April 14 to 25, 1985

Age Group, y	Survey 1			Survey 2		
	No. Who Drank	Medium No. of Cups	No. (%) Ill	No. Who Drank	Medium No. of Cups	No. (%) Ill
<1	3	...	1 (33)	0
1-4	14	2.0	5 (36)	21	3.5	4 (19)
5-9	22	4.0	7 (32)	21	2.0	4 (19)
10-19	55	2.5	3 (5)	64	3.5	8 (13)
20-29	37	2.0	6 (16)	64	2.0	6 (9)
30-39	32	1.3	2 (6)	47	1.3	4 (9)
40-49	32	3.0	3 (9)	47	1.0	8 (17)
50+	59	0.8	4 (7)	100	1.0	5 (5)
Total	254	...	31 (12)	364	...	39 (11)

Table 4.—Age Distribution of Salmonellosis in Outbreak Cases and in 1984 US *Salmonella* Surveillance Data

Age Group, y	%	
	March-April 1985 Outbreak (N = 11 502)	1984 US <i>Salmonella</i> Surveillance Data (N = 35 862)
<1	6.3	21.5
1-4	32.0	18.5
5-9	19.2	7.3
10-19	15.1	11.6
20-29	12.5	14.3
30-39	8.2	7.8
40-49	2.7	4.7
50+	4.0	14.2

severely affected (Table 4). Almost 5% of patients were employed in "critical occupations" (food handlers, health care workers, and day-care personnel) in which one might transmit the organism to others, and 15% of patients had a contact who was employed in a critical occupation. Sixteen percent of 9814 persons with information adequate for analysis had taken an antimicrobial in the month before onset of illness. Information on the specific antimicrobial taken was available for 1270 persons (81%); 90% had taken an antimicrobial to which the organism was resistant, 9% had taken an antimicrobial to which the organism was sensitive, and 1% had taken an antimicrobial to which the sensitivity of the organism was not tested. Twenty-two percent of 12 624 respondents were hospitalized. Information on antimicrobial use was available for 2049 hospitalized persons (73%); of these hospitalized patients, 479 (23%) had taken an antimicrobial in the month before illness. The hospitalization rate was 31% for persons who took an antimicrobial to which the organism was resistant and 24% for persons who took an antimicrobial to which the organism was sensitive. Reported complications included osteomyelitis (n=1), brain abscess (n=1), meningitis (n=2), and appendectomy (n=15). Eighteen deaths occurred, but a review

of death certificates suggested that *Salmonella* was the probable cause of death in two persons and possibly related in 12 other deaths. The IDPH also received reports of 1173 cases in residents of 17 other states. Most of these cases were in Indiana, Iowa, and Michigan, where the implicated milk was also distributed.

Laboratory Results

All *S typhimurium* isolates from cases and milk were resistant to ampicillin, tetracycline, carbenicillin, streptomycin, sulfisoxazole, erythromycin, sulfadiazine, penicillin, and a mixture of sulfabenzamide, sulfacetamide, and sulfathiazole (Sultrin), and sensitive to chloramphenicol, gentamicin, kanamycin, sulfamethoxazole and trimethoprim, cephalothin, nalidixic acid, and trimethoprim. The epidemic strain had a 140 megadalton (MDal), a 65 MDal, and a 2 MDal plasmid.

US Distribution.—None of the reference CDC or US Dept of Agriculture strains had exactly the same plasmid profile as the Illinois outbreak strain.

Wisconsin Distribution.—Only four isolates from Wisconsin residents with sporadic cases of *S typhimurium* had the outbreak antimicrobial-resistance pattern, and only two of these four had the outbreak plasmid profile; both patients had consumed brands A and B

2% milk products during an outbreak period (one in August 1984 and the other in March 1985).

Illinois Distribution.—Twenty-three of the 486 *S typhimurium* isolates collected from Illinois residents with salmonellosis between January 1984 and February 1985, excluding the outbreak period of August 1984, had the outbreak plasmid profile: these occurred in two main clusters with the onset of the earliest case on June 18, 1984 (Fig 2). For those persons with recorded shopping histories, 75% (9/12) of persons with *S typhimurium* with the outbreak plasmid profile and 54% (45/84) with sensitive *S typhimurium* had shopped at the implicated grocery store chain. The clusters of cases may represent small outbreaks.

Investigation of the Dairy Processing Plant

Salmonella typhimurium was isolated from three products: brand A 2% milk with a March 29, 1985, expiration date and from brand B 2% milk that was dated April 8 and 17. The April 17 product was recalled before it reached supermarket shelves. These three products were processed on March 20 and 30 and April 8. No *Salmonella* was isolated from 322 samples of other batches of milk from 13 of the 14 other production days between March 16 and April 8 or from numerous other pasteurized milk products of the implicated plant (including chocolate milk, milk shakes, ice cream products, eggnog, cultured milk products, and cottage cheese). None of 654 cultures of the dairy environment (taken after extensive cleaning) yielded *Salmonella*. *Salmonella* was isolated from 28 (5.5%) of 505 samples of pooled raw milk from 2786 milk producers in Wisconsin and northern Illinois, but none of the strains were identical to the outbreak strain.

Inspection of the dairy processing plant revealed a potential cross-connection (a skim milk transfer line) between tanks that contained raw milk and the pasteurized skim milk tank. This cross-connection was disconnected on April 3, 1985, reconnected on the evening of April 7, and disconnected on April 8, before milk processing began. However, the short length of pipe to which the distal end of the skim milk transfer line had been connected formed a dead space between a cap and a valve. Specialized testing demonstrated that under certain circumstances an unrepasteurized "reclaimed" product could bypass a pasteurizer and be pumped to the pasteurized skim milk tank. No salmonellae were found in tested samples of ingredients added to the milk,

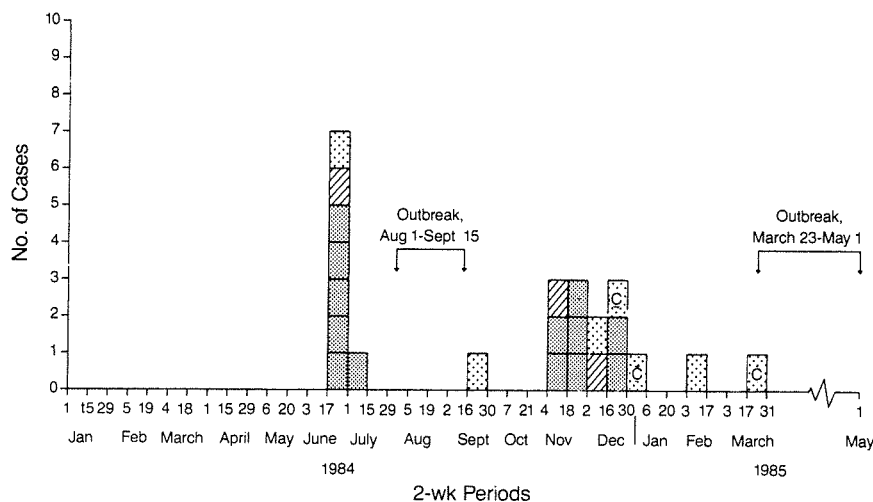


Fig 2.—Sporadic cases of *Salmonella typhimurium* gastroenteritis with outbreak-related plasmid profile by date of onset and source of dairy products, Jan 1, 1984, to March 22, 1985. Closely dotted bars indicate implicated store shopper; hatched bars, other store shopper; loosely spaced dotted bars, store unknown; and C, date of culture result.

such as vitamins, or in the packaging materials (paper and ink). Tests by the Food and Drug Administration and a private laboratory showed that the outbreak strain of *Salmonella* was heat sensitive and would not have survived pasteurization. The absence of detectable levels of phosphatase in tested samples of milk showed adequate pasteurization within the limits of the test sensitivity and that finished product could not have been contaminated with large volumes of raw milk. The Division of Criminal Investigation, Illinois Department of State Police, interviewed 129 present and former employees and found no indication that any had sabotaged the plant.

COMMENT

Although *S typhimurium* is the most common *Salmonella* serotype, the unusual antimicrobial-resistance pattern and plasmid profile of the epidemic strain enabled the investigators to examine stored and freshly isolated *Salmonella* from humans, animals, and milk and to trace the movements of the epidemic strain. A closely related *Salmonella* that differed from the epidemic strain only by having a kanamycin-resistance transposon caused a roast beef-associated outbreak at an Illinois college in April 1984. The epidemic strain itself first appeared in late June 1984, in a patient who routinely bought dairy products from the supermarket chain that sold the implicated plant's products. Between June 1984 and the massive outbreak that began in March 1985, the epidemic strain appeared in a large outbreak in which the dairy plant

was highly suspect and in two smaller clusters of cases that may represent small outbreaks that were not detected and investigated when they occurred (Fig 2). Finally, the epidemic strain contaminated the plant's milk on at least three dates in 1985 (March 20 and 30 and April 8), causing the largest outbreak of salmonellosis ever recorded in the United States. Since many different strains of *Salmonella* must have entered the plant repeatedly in raw milk but been killed by pasteurization, the persistence of the epidemic strain suggests that it persisted in the plant for almost ten months. The original source of this multiple-resistant strain may well have been dairy cattle; use of antimicrobials on dairy farms can lead to emergence of resistant strains.⁵

In this investigation, the niche (or niches) within the plant in which the epidemic strain may have persisted was not detected, and the precise method by which the milk was repeatedly contaminated could not be proved. However, the causes of contamination of the products are not a complete enigma. In most dairy plants, pasteurization is one of the last steps in processing. The implicated plant was unusual in that pasteurization was an early step in processing; it relied on careful postpasteurization handling of the milk during separation, blending, and other steps to prevent contamination of the final product. A few milliliters of highly contaminated milk (10^{8-10} salmonellae) mixed with previously pasteurized milk could cause the number of cases observed. *Salmonella*-contaminated reclaimed milk or raw milk could have moved into

the cross-connection between raw and pasteurized milk (the skim milk transfer line) and multiplied in the static milk given an appropriate temperature and sufficient time; this could have occurred during the interval before the blending of skim and whole milk to make 2% milk began each morning. The now heavily contaminated milk could have moved into the pipes used for blending when the rapid flow of milk exerted negative pressure. Only 2% milk would be heavily contaminated because it was the first product blended each day.

The major argument against this scenario is that the skim milk transfer line can account for the March 20 and 30, 1985, contaminations, but not for that on April 8, because it was disconnected on April 8, before milk processing began. However, milk could have entered the dead space in the short length of pipe to which the distal end of the skim milk transfer line had been connected, been contaminated by salmonellae that persisted on the internal surface of the threaded cap used to close the pipe during processing, and then allowed salmonellae to incubate before blending began.

The use in the month before illness of an antimicrobial to which the organism was resistant increased the risk of a symptomatic infection by this resistant *Salmonella* more than fivefold.^{6,9} Antimicrobial use may increase the risk of infection with resistant *Salmonella* through two different mechanisms: (1) by depleting the normal bowel flora and thus making the gut susceptible to a smaller dose of ingested *Salmonella* and (2) by giving a selective advantage to resistant *Salmonella* strains already colonizing the gut when the antimicrobial is taken. In this outbreak, ill persons who had been taking antimicrobials to which the organism was resistant had consumed significantly less milk than other ill persons, suggesting that the inoculum needed to cause disease was lower in persons who already were taking an antimicrobial. Since many persons who drank the contaminated milk would not have become ill if they had not been taking antimicrobials, the antimicrobial resistance of the epidemic strain increased the size of the outbreak. The number of excess cases attributable to the effect of taking antimicrobials can be calculated by using the relative risk (a measure of the strength of association of illness with antimicrobial use) and the proportion of the population taking antimicrobials; thus, we can estimate that 16% of the cases occurred because of antimicrobial use for some other condition, and would not have occurred

if the milk had been contaminated with a sensitive strain.

The two estimates of the actual size of the outbreak in Illinois derived from two telephone surveys were 168 791 and 197 581 cases. Despite the large numbers affected and the fact that 5% of those ill and 15% of contacts of ill persons were in critical occupations, no secondary food-borne or hospital outbreaks were reported. Specimens for culture were obtained from an unusually high percentage of ill persons, and a high percentage of cases were reported to public health officials. In previous outbreaks of salmonellosis, less than 1% of symptomatic infections are believed to have been reported,¹⁰ but about 10% of symptomatic infections

were reported in this outbreak. This tenfold improvement in case ascertainment may reflect both the impact of intense media publicity about the outbreak and the affected persons' desire to document their infections for medicolegal purposes.

The trend toward food production by a relatively small number of large companies rather than by many small businesses achieves economies of scale, permits maximum use of modern technology, and may ultimately decrease the amount of food-borne disease that occurs. However, large producers must be especially careful to prevent contamination of their products because the consequences of such contamination can be truly catastrophic.

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