Powdered Infant Formula as a Source of *Salmonella* Infection in Infants

Sarah M. Cahill,[1] I. Kaye Wachsmuth,[2] Maria de Lourdes Costarrica,[1] and Peter Karim Ben Embarek[3]

[1]Food and Agriculture Organization of the United Nations, Rome, Italy; [2]International Public Health Consultant, Private Practice, DeLand, Florida; and [3]World Health Organization, Geneva, Switzerland

Powdered infant formula is not sterile and may be intrinsically contaminated with pathogens, such as *Salmonella enterica,* that can cause serious illness in infants. In recent years, at least 6 outbreaks of *Salmonella* infection in infants that have been linked to the consumption of powdered infant formula have been reported. Many of these outbreaks were identified because the *Salmonella* strains were unique in some way (e.g., a rare serotype) and a well-established *Salmonella* surveillance network, supported by laboratories capable of serotyping isolates, was in place. Another common feature of the outbreaks was the low level of salmonellae detected in the implicated formula (salmonellae may be missed in routine testing). These outbreaks likely represent only a small proportion of the actual number of *Salmonella* infections in infants that have been linked to powdered infant formula. Managing this problem requires a multidimensional approach in which manufacturers, regulators, and caregivers to infants can all play a role.

Powdered infant formula (PIF) is not a sterile product and may be intrinsically contaminated with pathogens that can cause serious illness in infants (i.e., children aged <1 year). The potential for intrinsic contamination during production of PIF has been reviewed [1, 2], and several surveys of PIF provide an overview of the pathogens that may contaminate this infant foodstuff [3, 4]. In 2004, an expert meeting convened by the Food and Agriculture Organization of the United Nations and the World Health Organization concluded that the microorganisms of greatest concern in PIF are *Salmonella enterica* and *Enterobacter sakazakii* (table 1) [1, 2]. Intrinsic contamination of PIF with nontyphoid *S. enterica* is an important cause of infection and illness in infants [1]. Although the relatively recent emergence of *E. sakazakii* as a pathogen of human health concern, together with the severity of the disease it may cause in infants, has led to much discussion and research, concerns regarding *S. enterica* in PIF have been somewhat overshadowed. A review of the peer-reviewed literature revealed several large recent outbreaks of *Salmonella* infection among infants that were attributable to contaminated PIF, resulting in diarrhea and, in some infants, bacteremia and meningitis. Such outbreaks occurred even when the consumed PIF appeared to be in compliance with current international standards [5].

EPIDEMIOLOGY

In the United States, the incidence of salmonellosis (from all sources) among infants (121.6 laboratory-confirmed infections per 100,000 infants) was ~8 times greater than the incidence among other age groups [6]. Similarly high incidences of salmonellosis among infants have been reported elsewhere (e.g., 181 cases per 100,000 infants in the United Kingdom [7] and 92.8 cases per 100,000 infants in Israel [8]). Although data are not available for many countries and, particularly, for developing countries, nontyphoid salmonellosis is among the most common and widely reported of foodborne diseases [9, 10].

From a global perspective, it is not clear whether the higher incidence of salmonellosis among infants is the result of greater susceptibility or higher exposure or whether infants are simply more likely than persons in other age groups to seek medical care or have stool cultures performed [11]. However, when infected, it does appear that infants and young children, particularly those with immunocompromising conditions or those

Received 18 May 2007; accepted 29 September 2007; electronically published 12 December 2007.

Reprints or correspondence: Dr. Sarah M. Cahill, Food Quality and Standards Service, Nutrition and Consumer Protection Div., Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy (sarah.cahill@fao.org).

Clinical Infectious Diseases 2008; 46:268–73

1058-4838/2008/4602-0019$15.00
DOI: 10.1086/524737

Table 1. Categorization of the microorganisms or microbial toxins of concern in powdered infant formula [1, 2].

Category	Organisms
Clear evidence of causality	*Enterobacter sakazakii* and *Salmonella enterica*
Causality plausible but not yet demonstrated	*Pantoea agglomerans* and *Escherichia vulneris* (both formally known as *Enterobacter agglomerans*), *Hafnia alvei*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Citrobacter freundii*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia* species, and *Acinetobacter* species
Causality less plausible or not yet demonstrated	*Bacillus cereus*, *Clostridium difficile*, *Clostridium perfringens*, *Clostridium botulinum*, *Listeria monocytogenes*, *Staphylococcus aureus*, and coagulase-negative staphylococci

NOTE. Microorganisms were catergorized on the basis of the strength of evidence of a causal association between their presence in powdered infant formula and illness in infants [1, 2].

who are otherwise unwell, are more likely to experience severe illness or death due to salmonellae [12, 13].

SALMONELLOSIS LINKED TO DRIED MILK PRODUCTS: HISTORICAL PERSPECTIVE

Historically, *Salmonella* species–contaminated dried milk products caused recognized outbreaks of illness as early as the 1950s in the United Kingdom and Bulgaria [14]. In 1966, a multistate outbreak of *Salmonella* Newbrunswick infection, which primarily affected infants, occurred in the United States [15]. The outbreak investigation ultimately linked the illnesses to consumption of dried milk predominately from 1 manufacturer. *Salmonella* Newbrunswick was isolated from unopened containers, the manufacturing plant environment, and other milk products on the premises. Contamination apparently occurred in the spray driers [15].

Other large outbreaks have also been reported. In 1973, an island-wide outbreak of salmonellosis occurred on Trinidad in which ~3000 infants were infected with *Salmonella* Derby [16]. A retrospective investigation and case-control study linked illness to consumption of 7 brands of powdered milk packaged at a single processing plant, although no product was available for culture. In 1977, a major outbreak of *Salmonella* Bredeney infection that occurred in Australia was traced to contamination of powdered milk–based infant formulas during manufacture [17]. Similar to the outbreak of *Salmonella* Newbrunswick infection, investigation of the manufacturing conditions revealed that contamination occurred in the spray driers.

Incidents such as these led to the implementation of specific preventative measures, particularly during the 1970s, to minimize the risk of contamination of dehydrated dairy products with *Salmonella* species [15, 17]. A survey undertaken in the United States from 1967 through 1988 illustrated the positive impact of these measures in reducing the prevalence of salmonellae contamination of skim milk powder; the prevalence of such contamination decreased from a high of 1.9% in 1976 to 0.01% in 1988 [18].

SALMONELLA INFECTION ASSOCIATED WITH PIF: AN ONGOING PROBLEM

However, despite efforts to control salmonellae in dried milk–related products, in the 20-year period from 1985 through 2005, there were at least 6 outbreaks of *Salmonella* infection in infants that were linked to the consumption of PIF (table 2).

In 1985, an outbreak of *Salmonella* Ealing infection in the United Kingdom was linked to 1 brand of infant formula, and again contamination was traced back to problems in the spray drier [19]. The other significant feature of this investigation was the very low number of salmonellae estimated to be present in the powder (1.6 organisms per 450 g); a low number of salmonellae would have been difficult to detect by the quality-control sampling practiced at that time (using only 50-g samples) [19].

A report from the US Centers for Disease Control and Prevention in 1993 described infections with a lactose-fermenting strain of *Salmonella* Tennessee in the United States and Canada. The atypical organism was eventually isolated from the product and the manufacturing plant [20]. Soon after (in 1994), the Health Ministry in Spain reported 48 *Salmonella* Virchow infections, occurring in 14 of the 17 regions of Spain, mostly in children aged <7 months. The unique lactose-fermenting strain was also found in PIF, which was implicated through case-control studies [21]. Both of these outbreaks were caused by lactose-fermenting stains of *Salmonella* species. Because the inability to ferment lactose is often key in the identification of the *Salmonella* genus, the number of reported cases is probably much lower than the actual number of cases. In fact, a follow-up analysis of the Spanish outbreak concluded that it was more extensive than was initially thought [25].

The role of laboratory-based surveillance and targeted epidemiologic investigations was again highlighted in the detection of an outbreak of illnesses due to *Salmonella* Anatum in the United Kingdom and France during the period 1996–1997 [22]. In addition, during this outbreak, molecular subtyping was used

Table 2. Salmonellosis outbreaks during the period 1985–2005 that have been linked to powdered infant formula (PIF).

Salmonella serotype	No. of infants affected	Vehicle	Location	Year	Organism isolated from PIF	PIF implicated by epidemiologic study	Reference
Ealing	48	PIF	United Kingdom	1985	Yes	Yes	[19]
Tennessee	⩾3	PIF	United States, Canada	1993	Yes	Yes	[20]
Virchow	⩾48	PIF	Spain	1996	Yes	Yes	[21]
Anatum	17	PIF	United Kingdom, France	1996–1997	No	Yes	[22]
London	30	PIF	Korea	2000	Yes (open package only)	Yes	[23]
Agona	141	PIF	France	2004–2005	Yes	Yes	[24]
Total	⩾287	…	…	…	…	…	…

to more specifically identify the epidemic strain, and rapid communication and collaboration through the Salm-Net surveillance network were used to identify an international outbreak.

Epidemiologic studies of 30 cases of *Salmonella* infection in infants in Korea in 2000 concluded that the infections were a result of sporadic contamination of 1 particular brand of PIF that was consumed by all of the sick infants [23]. However, it was not possible to determine whether the PIF was contaminated during manufacture or after opening of the package for consumption, because the organism was only found in an opened package of formula. This highlighted the potential for contamination of PIF by the end user. Similarly, the investigation of an outbreak of infection due to *Salmonella* Saintpaul in a children's hospital in the United States in 2001 suggested that the source was formula prepared in the hospital's formula preparation room; however, it was not possible to determine whether the source was the PIF, the preparation utensils, or the environment [26]. In addition to implicating formula, this outbreak underlines the potential of reconstituted PIF to be a vehicle for salmonellae, even in cases in which the PIF is not the source of the organism.

The most recently reported outbreak of *Salmonella* infection, due to *Salmonella* Agona, was, in fact, 2 consecutive outbreaks linked to 2 brands of PIF that were manufactured on the same production line [24]. Although the source of contamination in the manufacturing plant is yet to be ascertained, a former and persistent environmental contamination is suspected. An important aspect highlighted by this outbreak was the international trade in PIF, implicating brands being exported to Asia, Africa, Oceania, and other European countries.

PUBLIC HEALTH PROBLEM

The incidence of salmonellosis among infants is higher than that among all other age groups. Six outbreaks of *Salmonella* infection associated with PIF during the period 1985–2005, involving ~287 infants, clearly indicate that contamination of PIF with *Salmonella* species contributes to the burden of salmonellosis among infants. Most of these outbreaks were identified because the *Salmonella* strains were unique in some way (e.g., the occurrence of a rare serotype or a distinguishing biochemical aberrancy [lactose fermentation]). In many regions of the world where *Salmonella* serotyping is not routinely performed and *Salmonella* surveillance networks are not established, identification of geographically and/or temporally diffuse outbreaks of *Salmonella* infection is difficult. Clinically, there are hospitalizations and even deaths attributable to *Salmonella* infection, but the majority of patients have a diarrheal illness, for which a culture might not be performed or which may remain unreported, even in a "sophisticated" children's hospital [26]. Consequently, outbreaks of salmonellosis attributable to contaminated PIF are likely to be underreported.

Even where surveillance systems are established and cases are identified, many clusters are likely to be unrecognized, because the existing surveillance systems are not sufficiently specific to detect them. This was highlighted by the outbreak of *Salmonella* Agona infection, in which a delay in the detection of the pathogen was partly linked to the detection algorithm of the surveillance system; this algorithm was based on the number of cases occurring among persons of all ages during the period of the outbreak, compared with during the same period in the previous 5 years [24]. Faster detection would have been facilitated by the continuous analysis of age-specific incidence rates.

A common feature in the reported outbreaks of *Salmonella* infection was the low levels of salmonellae found in the PIF. Such levels are not easy to detect and may be missed by some of the conventional methodology or the sampling plans currently used. In most of the investigations, the epidemic strain of *Salmonella* species was isolated from bulk, storage, and/or retail packaged samples. This was not achieved without a great deal of effort. There are no data available to adequately describe the distribution of salmonellae in PIF, but it is considered to be sporadic or heterogeneous, leading to difficulties in detection. For example, in the investigation of the outbreak of *Salmonella* Ealing infection, intensive bacteriological sampling by 33 laboratories found no pathogens in 4554 samples of 658

batches of product. Finally, 1 laboratory reported the isolation of *Salmonella* Ealing from an opened packet of PIF taken from an infected infant's home. This facilitated targeted testing based on a specific manufacturing code, leading to the isolation of *Salmonella* Ealing from 4 of 267 sealed packets [19]. This highlights the difficulty for food microbiology laboratories, which could not have cultured an adequate sample of products without a targeted strategy.

In terms of public health, it is worth noting that other pathogenic bacteria also contaminate PIF and may cause disease through consumption of PIF (table 1). Although these organisms have also been linked to infections in infants, they are even less likely to be identified, reported, or subject to an investigation to identify the source of infection. Investigations into cases or outbreaks of infant disease attributable to such organisms would be useful to establish whether PIF is a source of such infections.

RISK MANAGEMENT

Although the World Health Organization recommends that infants should be exclusively breast−fed for the first 6 months of life to achieve optimal growth, development, and health [27], there is recognition that this is not always feasible, and thus, infants who are not breast−fed require a suitable and safe breast milk substitute, such as PIF. The World Health Assembly in 2005 urged its members to take protective and preventive actions to minimize the exposure of infants to any hazards associated with PIF [28].

Addressing the problem of PIF-related salmonellosis in infants requires a multifaceted approach, particularly because the reported outbreaks indicate that low levels of salmonellae in PIF can lead to a substantial number of illnesses (table 2). Therefore, measures are needed at the manufacturing level to minimize the potential for intrinsic contamination of PIF with salmonellae and, subsequently, during preparation, storage, and handling of PIF to minimize the potential for contamination of the PIF from the environment and/or the growth of salmonellae in reconstituted PIF.

Currently, it is not technologically feasible to produce sterile PIF. Therefore, measures must focus on keeping levels of contamination of the product as low as possible. As such, control measures should concentrate on (1) avoidance of entry of salmonellae in the manufacturing environment, (2) avoidance of multiplication of salmonellae in case of entry, (3) hygienic design of equipment and high hygiene zones, and (4) use of dry-mixed ingredients that are free of salmonellae [2]. In addition, the lessons learned from previous outbreak investigations provide an informative basis from which manufactures can improve their control measures. Guidance in this regard is being incorporated into the revised International Code of Hygienic Practice for Powdered Formula for Infants and Young Children under development by the Codex Alimentarius. National authorities have a responsibility to ensure that the industry takes the necessary measures and meets the internationally established Codex criteria for salmonellae in PIF.

PIF is not a sterile product. Furthermore, there is risk of cross-contamination during preparation. Depending on storage and feeding practices, there is potential for rapid growth in reconstituted formula, amplifying what would otherwise likely be a very low level of contamination. The World Health Organization, in collaboration with the Food and Agriculture Organization of the United Nations, has recently issued new guidelines for the safe preparation, storage, and handling of powdered infant formula [29]. These guidelines have been developed to address the risks associated with the presence of both *S. enterica* and *E. sakazakii* in PIF and to highlight the role of good hygiene practices in the preparation of reconstituted PIF and good practices for its safe storage, transport, and use. These guidelines also suggest reconstitution of PIF with water at no less than 70°C as a means of practically eliminating the risk associated with these pathogens. Although concerns have been expressed regarding the impact of 70°C water on the nutrient content of PIF, a study undertaken by the US Food and Drug Administration indicated minimal impact [2]. Although the implementation of such guidance can greatly reduce risk, its execution is not always feasible, particularly in developing countries, where access to hygienic preparation facilities, clean water, or firewood is often limited.

Caregivers to infants should be aware that PIF is not a sterile product. Where feasible alternative sterile products can be considered for infants of higher susceptibility, including neonates aged ⩽28 days and preterm, low–birth weight, or immunocompromised infants. A recent case-control study indicating that consumption of reconstituted infant formula was one of a number of risk factors for *Salmonella* infection in infants also highlighted the protective role of breast−feeding [30, 31]. Thus, educational messages—both on infant feeding options and on the safe preparation, storage, and handling of PIF—are necessary risk-management measures. The recent international guidelines [29] and associated educational material should facilitate the implementation of such a measure.

CONCLUSIONS

Outbreaks of salmonellosis among infants that are linked to PIF are likely to be underreported. Nevertheless, they highlight the need to recognize PIF as a potential source of *Salmonella* infection in infants. Awareness of this potential is an important step in addressing such a public health problem.

Industry and regulators play the primary critical role in minimizing the risk of illness from consumption of PIF and ensuring that PIF is as safe as technologically possible. Caregivers to infants can also contribute to risk reduction. This can be

achieved through the education of caregivers so that they are aware that PIF is not sterile and may contain bacteria that can cause serious illness in infants, and that correct preparation, storage, and handling of reconstituted PIF reduces the risk of illness. Such education should target caregivers to infants both in institutional settings and in the home.

The reported outbreak investigations highlight the unique challenges associated with the detection and identification of an outbreak of PIF-related *Salmonella* infection from both an epidemiologic and analytical microbiological perspective. Awareness of these challenges is the first step to improving surveillance systems and commonly used analytical methodology, thereby facilitating faster recognition of such outbreaks. The value of an established surveillance system with supporting laboratories and linkage to food-control systems cannot be underestimated. Nevertheless, our knowledge of the burden of PIF-related salmonellosis in infants is still limited, particularly in developing countries. Learning from the outbreak investigations conducted to date may be a valuable starting point in developing or strengthening existing systems within countries. For example, countries could improve the detection of outbreaks by surveillance systems through the development of age-specific cluster-detection algorithms and efforts to improve the timeliness of serotyping, reporting, and investigation of human salmonellosis cases. The existing outbreak reports alert us to problems such as these and should be used to enable us to address them in a timely manner, with the aim of improved consumer protection and public health.

Acknowledgments

We thank the participants of the 2004 and 2006 Food and Agriculture Organization of the United Nations/World Health Organization expert meetings on *Enterobacter sakazakii* and *Salmonella* species in powdered infant formula.

Potential conflicts of interest. All authors: no conflicts.

References

1. Food and Agriculture Organization of the United Nations/World Health Organization. *Enterobacter sakazakii* and other microorganisms in powdered infant formula; meeting report. Microbiological Risk Assessment Series **2004**:6.
2. Food and Agriculture Organization of the United Nations/World Health Organization. *Enterobacter sakazakii* and *Salmonella* in powdered infant formula; meeting report. Microbiological Risk Assessment Series **2006**:10.
3. Iversen C, Forsythe S. Isolation of *Enterobacter sakazakii* and other Enterobacteriaceae from powdered infant formula milk and related products. Food Microbiol **2004**; 21:771–7.
4. Muytjens HL, Roelofs-Willemse H, Jaspar GH. Quality of powdered substitutes for breast milk with regard to the members of the family Enterobacteriaceae. J Clin Microbiol **1988**; 26:743–6.
5. Codex Alimentarius Commission. Recommended International Code of Hygienic Practice for Foods for Infants and Children. RCP 21–1979. Available at: http://www.codexalimentarius.net/download/standards/297/CXP_021e.pdf. Accessed 14 February 2007.
6. Centers for Disease Control and Prevention. FoodNet Annual Report. **2004**. Available at: http://www.cdc.gov/foodnet/annual/2004/Tables.pdf. Accessed 6 September 2007.
7. Skirrow M. A demographic survey of *Campylobacter, Salmonella,* and *Shigella* infections in England: a public health laboratory service survey. Epidemiol Infect **1987**; 99:647–57.
8. Weinberger M, Slonik-Isaac H, Shachar D, et al. *Salmonella enterica* serotype Virchow: epidemiology, resistance patterns and molecular characterisation of an invasive *Salmonella* serotype in Israel. Clin Microbiol Infect **2006**; 12:999–1005.
9. Galanis E, Lo Fo Wong DMA, Patrick ME, et al. Web-based surveillance and global *Salmonella* distribution, 2000–2002. Emerg Infect Dis **2006**; 12:381–8.
10. World Health Organization. Drug-resistant *Salmonella.* Fact Sheet No 139. Available at: http://www.who.int/mediacentre/factsheets/fs139/en/. Accessed 15 February 2007.
11. Food and Agriculture Organization of the United Nations/World Health Organization. Risk assessment of *Salmonella* in eggs and broiler chickens. Microbiological Risk Assessment Series **2002**:2.
12. Olsen SJ, Bishop R, Brenner FW, et al. The changing epidemiology of salmonella: trends in serotypes isolated from humans in the United States, 1987–1997. J Infect Dis **2001**; 183:753–61.
13. Galanakis E, Bitsori M, Maraki S, Giannakopoulou C, Samonis G, Tselentis Y. Invasive non-typhoidal salmonellosis in immunocompetent infants and children. Int J Infect Dis **2007**; 11:36–9.
14. Marth EH. Salmonellae and salmonellosis associated with milk and milk products: a review. J Dairy Sci **1969**; 52:283–315.
15. Collins RN, Treger MD, Goldsby JB, Boring JR, Coohon DB, Barr RN. Interstate outbreak of *Salmonella newbrunswick* infection traced to powdered milk. JAMA **1968**; 203:838–44.
16. Weissman JB, Deen RMAD, Williams M, Swanston N, Ali S. An island-wide epidemic of salmonellosis in Trinidad traced to contaminated powdered milk. West Indian Med J **1977**; 26:135–43.
17. Forsyth JRL, Bennett NMcK, Hogben S, et al. The year of the Salmonella seekers—1977. Aust N Z J Public Health **2003**; 27:385–9.
18. Mettler AE. Pathogens in milk powder—have we learned the lesson? J Soc Dairy Technol **1989**; 42:48–53.
19. Rowe B, Begg NT, Hutchinson DN, et al. *Salmonella* Ealing infections associated with consumption of infant dried milk. Lancet **1987**; 2:900–3.
20. Centers for Disease Control and Prevention. *Salmonella* serotype Tennessee in powdered milk products and infant formula—Canada and the United States, 1993. MMWR Morb Mortal Wkly Rep **1993**; 42:516–7.
21. Usera MA, Echeita A, Aladueña A, et al. Interregional foodborne salmonellosis outbreak due to powdered infant formula contaminated with lactose-fermenting *Salmonella virchow.* Eur J Epidemiol **1996**; 12:377–81.
22. Threlfall EF, Ward L, Hampton M, et al. Molecular fingerprinting defines a strain of *Salmonella enterica* serotype Anatum responsible for an international outbreak associated with formula-dried milk. Epidemiol Infect **1998**; 121:289–93.
23. Park JK, Soek WS, Choi BJ, et al. *Salmonella enterica* serovar London infections associated with consumption of infant formula. Yonsei Med J **2004**; 45:43–8.
24. Brouard C, Espié E, Weill FX, et al. Two consecutive large outbreaks of *Salmonella enterica* serotype Agona infections in infants linked to the consumption of powdered infant formula. Pediatr Infect Dis J **2007**; 26:148–52.
25. Usera MA, Rodriguez A, Echeita A, Cano R. Multiple analysis of a foodborne outbreak caused by infant formula contaminated by a atypical *Salmonella virchow* strain. Eur J Clin Microbiol Infect Dis **1998**; 17:551–5.
26. Bornemann R, Zerr DM, Heath J, et al. An outbreak of *Salmonella* serotype Saintpaul in a children's hospital. Infect Control Hosp Epidemiol **2002**; 23:671–6.

27. World Health Organization. The global strategy for infant and young child feeding. **2002**. Available at: http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/gs_iycf.pdf. Accessed 6 September 2007.
28. World Health Assembly (WHA). WHA resolution 58.32. Infant and child nutrition. **2005**. Available at: http://ftp.who.int/gb/ebwha/pdf_files/WHA58/WHA58_32-en.pdf. Accessed 6 September 2007.
29. World Health Organization. Safe preparation, storage and handling of powdered infant formula: guidelines. **2007**. Available at: http://www.who.int/foodsafety/publications/micro/pif_guidelines.pdf. Accessed 11 May 2007.
30. Ingram LA, Fullerton KE, Marcus R, et al. A case-control study of Salmonella infection in infants, FoodNet, 2002–2004. Available at: http://www.cdc.gov/enterics/publications/126-Ingram_IDSA_2005pdf.pdf. Accessed 3 December 2007.
31. Rowe SY, Rocourt JR, Shiferaw B, et al. Breast-feeding decreases the risk of sporadic salmonellosis among infants in FoodNet sites. Clin Infect Dis **2004**; 38:S262–70.