Prevention of Invasive *Cronobacter* Infections in Young Infants Fed Powdered Infant Formulas

**WHAT'S KNOWN ON THIS SUBJECT:** Invasive *Cronobacter* infection is a rare but devastating disease known to affect hospitalized premature or immunocompromised infants fed powdered infant formulas (PIFs). PIF labels imply that powdered formulas are safe for healthy, term infants if the label instructions are followed.

**WHAT THIS STUDY ADDS:** *Cronobacter* can also infect healthy, term infants in the first months of life, even if PIF label instructions are followed. Invasive *Cronobacter* infection is extremely rare in exclusively breastfed infants or those fed commercially sterile, ready-to-feed formulas.

**abstract**

**BACKGROUND:** Invasive *Cronobacter* infection is rare, devastating, and epidemiologically/microbiologically linked to powdered infant formulas (PIFs). In 2002–2004, the US Food and Drug Administration advised health care professionals to minimize PIF and powdered human milk fortifier (HMF)’s preparation, feeding, and storage times and avoid feeding them to hospitalized premature or immunocompromised neonates. Labels for PIF used at home imply PIF is safe for healthy, term infants if label instructions are followed.

**METHODS:** 1) Medical, public health, Centers for Disease Control and Prevention, US Food and Drug Administration, and World Health Organization records, publications, and personal communications were used to compare 68 (1958–2003) and 30 (2004–2010) cases of invasive *Cronobacter* disease in children without underlying disorders. 2) The costs of PIFs and ready-to-feed formulas (RTFs) were compared.

**RESULTS:** Ninety-nine percent (95/96) of all infected infants were <2 months old. In 2004–2010, 59% (17/29) were term, versus 24% (15/63) in 1958–2003; 52% (15/29) became symptomatic at home, versus 21% (13/61). Of all infected infants, 26% (22/83) had received breast milk (BM), 23% (19/82) RTF, and 90% (76/84) PIF or HMF. Eight percent received BM and not PIF/HMF, 5%, RTF without PIF/HMF. For at least 10 PIF-fed infants, label instructions were reportedly followed. Twenty-four ounces of milk-based RTF cost $0.84 more than milk-based PIF; 24 ounces of soy-based RTF cost $0.24 less than soy-based PIF.

**CONCLUSIONS:** *Cronobacter* can infect healthy, term (not just hospitalized preterm) young infants. Invasive *Cronobacter* infection is extremely unusual in infants not fed PIF/HMF. RTFs are commercially sterile, require minimal preparation, and are competitively priced. The exclusive use of BM and/or RTF for infants <2 months old should be encouraged. *Pediatrics* 2012;130:1–9
Cronobacter multispecies complex, formerly classified as Enterobacter sakazakii (Cronobacter), are pathogenic, Gram-negative, non–spore-forming, coliform enteric bacteria. Invasive Cronobacter infection was first reported in 1961 and is now recognized as a rare, often devastating, infection predominantly affecting infants. Cronobacter infection appears to have a low infectious dose and short incubation period and (R. Mittal, PhD, personal communication, 2011). Liquefying meningitis is a frequent complication, and severe neurologic impairment or death is common. In the United States, only 1 state, Minnesota, requires Cronobacter reporting. These infections are likely underrecorded, as evidenced by recent events. In late 2011, single reports of Cronobacter illness in infants in Missouri and Illinois caused the Centers for Disease Control and Prevention (CDC) to ask public health officials around the country to look for other cases of Cronobacter infection among infants. This generated reports of 2 additional cases, 1 in Oklahoma and 1 in Florida, bringing the 2011 US case total to 13,10,11 Ten NICU Cronobacter outbreaks have been reported. In 8, nutritional sources were evaluated; all affected infants had received some specific powdered infant formula (PIF). In 3 outbreaks, epidemiological and microbiologic studies were done. There was no evidence of infant-to-infant or environmental transmission and the implicated PIF yielded Cronobacter.12–14 These findings, non–outbreak cases, and a 2002 US Food and Drug Administration (FDA) study isolating Cronobacter from 23% of sampled PIFs prompted the World Health Organization (WHO) to state: “Contaminated powdered infant formula has been convincingly shown, both epidemiologically and microbiologically, to be the vehicle and source of infection in infants.”

A 2002 FDA Letter to Health Care Professionals and subsequent cautionary material from formula manufacturers and the International Formula Council (see, for example, references 18 and 19) warned that premature infants and infants with underlying medical conditions could become infected with Cronobacter, recommended PIF be avoided in NICUs unless there was no alternative, and suggested the chance of infection could be decreased by (1) reconstituting only a small amount of formula at a time, (2) minimizing “holding time” between preparation and feeding, (3) refrigerating and using formula within 24 hours after preparation, and (4) not exceeding 4 hours “hang time” for continuous enteral feeding. Parents did not receive similar information but formula companies gradually changed PIF instructions and labels for at-home use to indicate that PIF should not be fed to premature or immunocompromised infants and, for infants’ safety, caretakers should (1) feed PIF immediately or refrigerate and use it within 24 hours and (2) use warmed formula within 1 hour or discard it. (see, for example, references 20–22) Since 2004–2005, PIF labels have stated that PIF is not sterile but, in a 2005–2006 US national survey, when mothers of 2-month-old infants were asked if various formulas were “likely to contain germs,” only 29.5% responded affirmatively for PIF, whereas 31.1% did so for commercially sterile, ready-to-feed formula (RTF), and 35.0%, for commercially sterile concentrates.

In an August 28th, 2003 letter to the FDA, the American Academy of Pediatrics (AAP) wrote, “While sampling large batches of product can be problematic, and product sterility cannot be absolutely assured, all powdered formula should be E. sakazakii free. The AAP also recommends that the standards regarding powdered formula be the same for premature as well as term infants. The AAP sees no reason that they should be different, as the absolute risk, even to term infants, is not zero.”

This study analyzes all obtainable 1958–2010 reports of invasive pediatric Cronobacter infection occurring worldwide in children without underlying disorders, to examine if the frequency, place of occurrence, or characteristics changed after warnings were disseminated to health care professionals. In addition, the costs of PIF, RTF, and concentrates were compared to determine if the latter 2 might be economically viable home-use alternatives to PIF for young infants who are not exclusively breastfed (EBF).

METHODS

Reviewed material included (1) CDC and FDA files obtained through Freedom of Information Act requests, (2) published cases and literature reviews, (3) all cases reported by WHO as of July 15 to 18, 2008, (4) personal communications with publication authors, and (5) nonconfidential information from parents, medical records, and legal documents. Children were not included in these analyses if their infections were noninvasive or they had underlying birth defects, medical conditions, or signs of immunodeficiency. Other exclusion criteria are provided in Supplemental Information 1. Of note, all children meeting these criteria were ≤87 days of age at symptom onset.

Definitions for terms used herein include the following: healthy, no recorded evidence of a preexisting immunodeficiency, underlying disorder, or birth

The proportion of infected infants who were neonates (83%) was stable (Table 1). Only 1 infant was >2 months old at symptom onset. During both time periods, the proportions of *Cronobacter*-infected infants who were premature and/or of low birth weight were higher than in the general population (prematurity, 13%; low birth weight, 8%); however, the proportions of cases involving term and normal birth weight infants were significantly higher in 2004–2010, compared with 1958–2003. Similarly, the proportion of invasive *Cronobacter* infections occurring in a hospital exceeded the proportion of US infants requiring prolonged postnatal hospitalization (29%), but the majority of 2004–2010 infections occurred at home, even though 2 infants who became symptomatic at home on the day of postnatal discharge were placed into the “hospital” category for this analysis. Consistent with these findings, the proportion of reported invasive *Cronobacter* infections involving necrotizing enterocolitis was lower in 2004–2010 than in 1958–2003. In both time periods, most reported *Cronobacter*-infected infants had meningitis.

Nutritional information (Table 2) was wholly absent for 19% of cases in 1958–2003 and no case in 2004–2010. Ninety percent of invasively infected infants had received a powdered product, that is, PIF or human milk fortifier (HMF). This proportion did not differ significantly between time periods, but in 2004–2008 proportionately more infants received multiple types of nutrition. Nineteen infants received RTF; where timing was specified, RTF was initiated before postnatal discharge; at least 9 infants were not receiving it on the day they became symptomatic. The proportions EBF (1/53 in 1958–2003 and 2/29 in 2004–2010) were much lower than the rate for all US neonates

**RESULTS**

The proportion of invasively infected infants with a preexisting disorder/immunodeficiency did not change significantly between 1958–2003 and 2004–2010 (9/77, 12% vs 6/36, 17%) and was higher than the general population rate (<5%). The worldwide average annual number of reported invasive *Cronobacter* infections in infants without preexisting conditions, that is, those examined further herein, was 1.5 in 1958–2003 (68 cases in 46 years) and 4.3 in 2004–2010 (30 cases in 7 years).

<table>
<thead>
<tr>
<th>Characteristica</th>
<th>1958–2003</th>
<th>2004–2010</th>
<th>Total</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>48/63 (76%)</td>
<td>12/29 (41%)</td>
<td>60/92 (65%)</td>
<td>NS</td>
</tr>
<tr>
<td>BW &lt;2500 g</td>
<td>15/63 (24%)</td>
<td>17/29 (59%)</td>
<td>32/92 (55%)</td>
<td>0.02</td>
</tr>
<tr>
<td>BW ≥2500 g</td>
<td>44/55 (80%)</td>
<td>10/24 (42%)</td>
<td>54/78 (68%)</td>
<td>NS</td>
</tr>
<tr>
<td>Premature, BW &lt;2500 g</td>
<td>42/54 (78%)</td>
<td>8/24 (33%)</td>
<td>50/78 (64%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Premature, BW ≥2500 g</td>
<td>6/54 (11%)</td>
<td>14/24 (58%)</td>
<td>20/78 (26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Place of symptom onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>48/61 (79%)</td>
<td>14/24 (48%)</td>
<td>62/80 (79%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Home</td>
<td>13/61 (21%)</td>
<td>15/29 (52%)</td>
<td>28/80 (35%)</td>
<td></td>
</tr>
<tr>
<td>Diagnoses&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>38/68 (56%)</td>
<td>22/30 (73%)</td>
<td>60/98 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>21/68 (31%)</td>
<td>14/30 (47%)</td>
<td>35/98 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>NEC</td>
<td>22/68 (32%)</td>
<td>1/30 (3%)</td>
<td>23/98 (23%)</td>
<td>0.001</td>
</tr>
<tr>
<td>UTI</td>
<td>1/68 (2%)</td>
<td>0/30 (0%)</td>
<td>1/98 (1%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

See Methods section and Supplemental Information 1 for details concerning data sources and selection criteria. BW, birth weight; NEC, necrotizing enterocolitis; NS, not significant; UTI, urinary tract infection.

p An infant was considered term if the records indicated that was the case and/or the gestational age was ≥37 weeks. An infant was considered premature if the records indicated that was the case and/or the gestational age was <37 weeks. Table excludes patients for whom the specified data are unknown; there were a total of 68 infants in 1958–2003 and 30 in 2004–2010.

p Fisher exact tests and Freeman-Halton extension of the Fisher exact probability test for a × 3 table. Not significant if \( P \geq 0.05 \). Totals percents may not equal 100 because of rounding.

p Term, BW <2500 g or premature, BW ≥2500 g. When “other” category is excluded, \( P \) remains <0.001.

p This category includes 1 infant who became ill 12 hours after leaving the hospital and another who was noted to be ill on the day of hospital discharge and was reportedly symptomatic while in the hospital.

p Some patients had >1 diagnosis. Specifically, 18 patients with meningitis also had proven bacteremia and 2 also had NEC. One patient with bacteremia also had NEC and one also had a UTI. \( P \) values are for proportion with each individual diagnosis.
in the denominator of received PIF but without information concerning what, if any, enteral feeding she did receive (AZ 2009). This infant is included nutrition noted.

BM, no PIF/HMFb 3/53 (6%) 4/29 d (14%) 7/82 (8%) NS
BM & HMF 3/53 (6%) 2/30 (7%) 5/83 (6%) NS
PIF, no BMb 43/53 (81%) 17/30 (57%) 60/83 (72%) .022
Not indicated 13/68 (19%) 0/30 (0%) 13/98 (13%)
Any RTFe 6/53d (9%) 13/29 d (45%) 19/82 (23%) .003
Any BMIe 10/54d (18%) 12/29 d (41%) 22/83 (26%) .036
Any PIF or HMFe 51/54d (94%) 25/30 d (83%) 76/83 (90%) NS
Notedd 55/68 (81%) 30/30 (100%) 84/98 (86%) .020

See Methods section and Supplemental Information 1 for details on data sources and selection criteria. Pertinent details on individual cases are provided in the Supplemental Information, but not all previously published details concerning outbreak-associated cases are provided therein. NS, not significant.

a Documented nutrition at any time before onset of symptoms, based on the best available information, including from medical records, CDC files, parent report, publications, and communications with publication authors. Total percent may not equal 100 because of rounding. Denominators include only those for whom data were known.

b The “PIF, no BM” category includes 9 infants who were also fed RTF, 7 of whom were not receiving RTF at the time of symptom onset and 2 of whom also received concentrate. One of these 2 was receiving only concentrate on the day of symptom onset.

The “BM & PIF” category includes 4 infants who also received RTF, one of whom additionally received concentrate. The “BM, no PIF/HMF” category includes 4 infants who were also fed RTF; one of them may also have been fed his twin’s PIF (see Supplemental Information 2 for details).

f Fisher’s exact test. Not considered significant if P ≥ .05.

This category includes 1 infant who received formula that was likely but not de

Note that a bottle nipple was positive

Cronobacter

a

isolate indistinguishable from the patient(s)” isolate(s) in 9 (75% of positive) incidents involving 35 patients. Environmental testing was never described in detail but was noted to have been done in 17 incidents involving 28 patients, with something positive in 6 (35%) incidents involving 16 (57%) patients. These involved formula preparation areas (sink, splash area, counter, water storage area, dish drawer); 2 were considered indistinguishable from patient isolates. FDA records for 1 case indicate that a bottle nipple was positive for Cronobacter in another, a pacifier. (See Supplemental Information 3 for summaries of available microbiologic information, including the techniques used by investigators to compare isolates.)

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The “BM & PIF” category includes 4 infants who also received RTF, one of whom additionally received concentrate. The “BM, no PIF/HMF” category includes 4 infants who were also fed RTF; one of them may also have been fed his twin’s PIF (see Supplemental Information 2 for details).

f Fisher’s exact test. Not considered significant if P ≥ .05.

This category includes 1 infant who received formula that was likely but not definitively PIF and definitely did not receive BM (J. Burdette, MD, personal communication, 2011). This infant is included in the denominator for “any BM” and not in any numerators. The category also includes an infant who defined as received a recalled, contaminated lot of PIF but I could not determine if he received BM or other formulas as well (Belgium 2002). This infant is included in the numerator and denominator for “any PIF.” A third infant in this category is a term newborn recorded on a CDC line list as not having received PIF but without information concerning what, if any, external feeding he did receive (AZ 2009). This infant is included in the denominator of “Any PIF or HMF” and is not included in “Any BM,” “Any RTF,” and “Any concentrate.”

g Categories are not mutually exclusive; therefore, total percent is >100. Numbers are for those who had the specified nutrition noted.

(48%), but the proportions who had been fed BM and other nutrition were not (9/54 = 17% and 10/29 = 34%, vs 23%).”29 The EBF-infected infants lived in Brazil (2003), India (2006), and Slovakia (2006). One US neonate diagnosed on the day of his postnatal discharge (2007) and 3 hospitalized infants (United States 1998–2001, United States 2003, Spain 2007) were fed only BM and RTF. Supplemental Information 2 provides the available case-specific clinical, epidemiological, and microbiologic testing details, broken down by nutrition received.

BM was cultured and negative in 5 cases, breast pumps in 2, and pump tubing in 1. Water samples were tested and negative in 10 PIF-related incidents involving 29 patients. One or more PIF product samples of some sort were Cronobacter tested in 29 incidents involving 62 patients and positive in 12 of the incidents (41%), involving 44 of the patients (71%). Investigators considered a Cronobacter isolate indistinguishable from the patient(s)’ isolate(s) in 9 (75% of positive) incidents involving 35 patients. Environmental testing was never described in detail but was noted to have been done in 17 incidents involving 28 patients, with something positive in 6 (35%) incidents involving 16 (57%) patients. These involved formula preparation areas (sink, splash area, counter, water storage area, dish drawer); 2 were considered indistinguishable from patient isolates. FDA records for 1 case indicate that a bottle nipple was positive for Cronobacter in another, a pacifier. (See Supplemental Information 3 for summaries of available microbiologic information, including the techniques used by investigators to compare isolates.)

Records for 4 hospital and 11 at-home US cases unrelate to outbreaks contained comments concerning the caretakers’ PIF or HMF feeding and storage techniques (15/35, 43%). For 1 hospitalized infant, it was noted that BM/HMF feedings were given over 30 minutes; for another, that 6 hours-worth of PIF was mixed at a time, refrigerated for <24 hours, and warmed immediately before feeding. For the remaining 2, BM and HMF were mixed immediately before feeding, hang time was <4 hours, and BM was either stored frozen or refrigerated for <6 hours. Records of 8 infants who became symptomatic at home specified that PIF was mixed immediately before each feeding and never stored; another infant’s parent made 2 bottles at a time, fed 1 immediately, and stored the other in the refrigerator just until the next feeding; another parent usually mixed formula for each feeding, occasionally made 1 or 2 extra bottles, stored these in the refrigerator, and used them within the day. In addition, 7 records specifically noted that unfinished remainders of feedings were always discarded; 5, that hands and/or preparation areas were washed before PIF preparation; and 6, that bottles, caps, and nipples were sterilized. Of note, these data were not collected systematically by case investigators and absence of information from a record does not indicate that a guideline was not followed. To summarize, for at least 2 infected, hospitalized infants, FDA guidelines reportedly were followed; for at least 10 infants infected at home, label instructions reportedly were followed.

Table 3 provides September 2011 on-line-shopping costs and relative costs for 6 formulas commonly used from birth to 6 or 12 months of age. These products are all available in PIF, RTF, and concentrate formulations. Prices varied relatively widely within and among brands, products, formulations, and stores. The cost of formula every 4 hours costs of feeding a neonate the least expensive
PIF and soy-based RTF, 24 cents less a day than soy-based PIF.

**DISCUSSION**

The major findings in this study are that the majority of reported invasive pediatric *Cronobacter* infections now occur in nonhospitalized and term infants, 99% were <3 months old, and 90% had received PIF. These findings raise a number of issues, including study limitations, potential sources of *Cronobacter* infection other than PIF and related to PIF, and implications in terms of parent education and infant feeding, taking into consideration that approximately half of US parents (those living at or below 185% of the federal poverty level) receive nutrition assistance through the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).

This study has at least 5 limitations. First, these data span a wide time period, during which NICU care, infant-feeding practices, and formula processing have changed in ways that cannot be fully addressed in these analyses. Second, I could examine only available records from known cases of invasive *Cronobacter* infections. Europe has a surveillance system for product contamination (European Rapid Alert System for Food and Feed), but few countries have active surveillance for clinical *Cronobacter* infections. Current automated bacterial identification systems can accurately identify *Cronobacter* but several cases’ medical records suggest that not all health care providers recognize that *Cronobacter* is an unusual pathogen. Cases reported after a public health alert support that health authorities are not proactively informed of all *Cronobacter* infections. Third, reporting may be biased in regard to case characteristics and information collected. For example, most neonatologists are likely aware of *Cronobacter* infection in premature infants. This might lead to better reporting from NICUs and a relative underestimation of infections in healthy, nonhospitalized infants. Also, infections in breastfed infants are disproportionately represented in published case

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**TABLE 3 Per Ounce Prices and Price Differences, by Brands and Forms of Infant Formulas**

<table>
<thead>
<tr>
<th>Type of Infant Formula</th>
<th>Price Rangea</th>
<th>Mean (Median) Cost Differences Compared With Powdered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td><strong>Within-brand differences</strong>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk-based formulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.121–0.192</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.156–0.417</td>
<td>26–60</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.137–0.193</td>
<td>11–15</td>
</tr>
<tr>
<td>Soy-based formulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.140–0.198</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.150–0.451</td>
<td>6–82</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.140–0.398</td>
<td>30–36</td>
</tr>
<tr>
<td>Prices for all brandsc</td>
<td>Mean (Median)</td>
<td></td>
</tr>
<tr>
<td>Milk-based formulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.160 (0.162)</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.237 (0.206)</td>
<td>48 (27)</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.180 (0.184)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Soy-based formulas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.170 (0.171)</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.232 (0.203)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.224 (0.212)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Both milk- &amp; soy-based combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.165 (0.169)</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.235 (0.203)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.202 (0.192)</td>
<td>22 (14)</td>
</tr>
<tr>
<td><strong>Least-expensive available productsd</strong></td>
<td>Actual cost/ounce</td>
<td>Actual Cost Differences Compared With Powdered</td>
</tr>
<tr>
<td>Milk-based formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.121</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.156</td>
<td>29</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.137</td>
<td>13</td>
</tr>
<tr>
<td>Soy-based formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powdered</td>
<td>0.140</td>
<td>NA</td>
</tr>
<tr>
<td>RTF</td>
<td>0.130</td>
<td>–7</td>
</tr>
<tr>
<td>Concentrate</td>
<td>0.140</td>
<td>0</td>
</tr>
</tbody>
</table>

Costs were determined for 6 formulas available for neonates and young infants (and for use by a premature or immuno-compromised infant as/10 recommended by that infant’s pediatrician): Enfamil (milk-based); 3 stores for PIF and RTF, 2 stores for concentrate); PreSobee UPI (soy-based) (5 stores for PIF, 3 stores for RTF, and 2 stores for concentrate); Good Start with iron, Gentle or Gentle plus (milk-based) (5 stores for PIF, 4 stores for RTF, and 3 stores for concentrate); Good Start soy. Supreme or Supreme Plus (4 stores for PIF, 3 stores for RTF, and 2 stores for concentrate); Similac Advance (milk-based) (5 stores for PIF, RTF, and concentrate); and Isomil (soy-based) (5 stores for PIF, 4 for RTF and concentrate). Prices were obtained in September 2011, for the least expensive packaging options, from the following Internet sites: Amazon.com, Babies-R-Us, CVS, Diapers.com, and Walmart. Not all sites carried all brands of each product, but all sites carried at least 1 brand each of a powdered, RTF, and concentrate product. Price ranges are for any of the assessed brands at any of the assessed Internet sites. NA, non applicable.

a In dollars per fluid ounce of prepared formula
b Brand-specific ranges for differences in mean and median costs of each product type (RTF and Concentrate), compared with PIF, by using prices from all stores carrying the specific product type. Median values are in parentheses.
c All brands of specified product type are included in analyses. Medians are provided in parentheses.
d Lowest priced product of any brand, at any store. Numbers reflect actual costs and cost differences for those products.

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**formula of each type were compared. Milk-based RTF cost 84 cents more a day than milk-based PIF and milk-based concentrate cost 38 cents more than milk-based PIF. Soy-based concentrate cost no more than soy-based**
reports, even though these provide no or minimal epidemiological or environmental microbiological data, whereas infections in PIF-fed infants dominate CDC records, review articles, and footnotes in published microbiologic studies. Fourth, information concerning feeding preparation and storage techniques was not provided in response to standardized questionnaires and therefore is incomplete and varies between records. Fifth, I could not document data validity. Much information was obtained by public health investigators at the time of the illness, but some preparation and storage information was obtained in subsequent years. Parental recall may have been inaccurate or influenced by grief, stress, and/or a sense of guilt.

For 3 cases involving PIF-fed infants at home, *Cronobacter* was isolated from kitchen surfaces, for another, from a pacifier; and, for a fifth, from a bottle nipple. Epidemiological investigations could not determine whether these were contaminated by PIF or reflected an extrinsic source of PIF contamination or infection. *Cronobacter* has been found in a number of food substances, some used in PIF and some commonly present in household kitchens. In a recent study, it was recovered from environmental sampling in 21 of 78 kitchens of recruited, predominantly low-income, middle Tennessee households. These findings, the seven reported cases of invasive infection in non-PIF-fed infants, and occasional *Cronobacter* infection or colonization of immunocompromised, hospitalized adults, indicate that *Cronobacter* infections are sometimes related to non-PIF sources. However, epidemiological and microbiologic data strongly implicate PIF as a source of pediatric *Cronobacter* infections. Furthermore, *Cronobacter* has been isolated repeatedly from PIF, including as recently as 2010. *Enterobacteriaceae* are established and ubiquitous in PIF dry processing environments; eradication is not considered possible. PIF, RTF, and concentrate manufacturing begin with nonsterile nutritional components being put into solution, homogenized, and then pasteurized, resulting in commercial sterility. PIF is then dried in a nonsterile environment and nonsterile components often are added after pasteurization. Drying and dry-processing areas can be kept free of *Salmonella* through environmental, component, and end-product surveillance and microbiologic testing; however, 6 PIF-associated salmonellosis outbreaks have been reported since 1995, in Canada, France, Korea, Spain, the United Kingdom, and the United States. The most recent, in 2005, involved 141 French infants.

One of the statistical assumptions in the FDA’s *Cronobacter* end-product testing protocol is that *Cronobacter* contamination in PIF is not clustered or clumped; however, *Cronobacter* has been described as tending to form clumps that are “sort of stuck together.” A recent study provided evidence of this. A 22,000 kg, released-to-market lot (ie, batch) of PIF was recalled because postmarket testing by authorities found 1 package to be positive for *Cronobacter*. Examination of the retrieved material showed that contamination varied among production-time-specific samples. Most samples were below detectable limits but 3- to 560-cell clusters occurred sporadically in 8 of 2290 1-g samples. The 2 largest clusters, of 123 and 560 cells, originated from just 2 product bags. Of note, the investigated lot contained >1 contaminated product bag, but that does not preclude the possibility of more confined, even single-bag, contamination occurring in other lots of PIF. *Cronobacter* has never been isolated from BM, unopened bottled water, treated US municipal drinking water, unopened RTF, or unopened concentrates. Only 7 reported, invasively infected infants were not fed PIF. PIF labels imply the product is safe if label feeding and storage instructions are followed. AAP and WHO PIF guidelines recommend cleaning hands and preparation areas, cleaning and sterilizing equipment, discarding unfed warmed, prepared formula after 2 hours, and storing prepared formula in a refrigerator and for no more than 24 hours. Cases of invasive *Cronobacter* infections have occurred when these preparation and feeding guidelines, as well as label directions, reportedly were followed or exceeded (in that formula was always prepared as individual servings immediately before feeding and never stored). WHO guidelines also recommend that water be boiled and cooled for up to 30 minutes before being added to PIF to achieve a reconstitution temperature of 70°C, because WHO consultants determined this inactivated all tested *Cronobacter* strains. Not all organizations agree with this recommendation.

In 2002, the FDA and the US Department of Agriculture reversed their own recommendations that health professionals use boiled water to reconstitute PIF, citing potential loss of heat-sensitive nutrients, changes in some formulas’ physical characteristics, inadequate destruction of *Cronobacter*, and injury to personnel preparing formula. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition also disagreed with the WHO recommendation, because of possible adverse effects on nutrients. AAPs’ current instructions do not recommend boiling water unless the safety of the water source is uncertain. Two case records reviewed herein indicated that the *Cronobacter*-infected infants had received boiled water, but there was no indication it was done as recommended by WHO. Of note, in a recent report of two 2010 noninvasive
Cronobacter infections in Mexico, associated with a US-manufactured PIF, the authors determined that the health care providers had attempted to follow WHO guidelines. However, retrospective investigation suggested that the boiled water was likely 45°C, not 70°C, at the time of PIF reconstitution.9

The AAP recommends exclusive breastfeeding for the first 6 months of infancy.46 The data herein suggest that invasive Cronobacter infection rarely occurs in EBF infants. However, the proportion of Cronobacter-infected infants who were partially breastfed was similar to the rate for all US 1-month-olds. In a 2007 survey of breastfeeding-related maternity practices at US hospitals and birth centers, 70% of facilities reported providing breastfeeding mothers with discharge packs containing formula samples.47 It might be helpful to discontinue these samples or limit them to RTF, which is commercially sterile, requires minimal, albeit careful, handling, and is comparably priced to PIF if parents are willing and able to comparison shop.

Comparison shopping is not a primary option for families on WIC. WIC has instituted policies to encourage breastfeeding, with some apparent success; in 1 non-nationally representative, US survey, 47% of WIC neonates were EBF in the previous week, compared with 26% of non-WIC neonates.23 Infant formula is purchased by WIC at a discount, through a state-by-state exclusive contract bidding process, and provided to nonbreastfeeding or BM-supplementing mothers. RTF is available through WIC, but PIF is the predominant type of formula currently used by the program. The options for parents on WIC could be improved if WIC could provide RTF for infants in the first 2 months of life.

CONCLUSIONS
Premature and immunocompromised PIF-fed neonates continue to be disproportionately represented in reports of invasive Cronobacter infection, relative to their proportion in the general population. However, the majority of cases now involve nonhospitalized and term, PIF-fed infants. Parents, like health care professionals, need education concerning the proper handling and storage of infant nutrition, as well as accurate information concerning the relative number of enteric infections, including Cronobacter; in EBF, RTF-fed, and PIF-fed infants, so they can make informed decisions about their infants’ nutrition.

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