

23-ID-03**Committee:** Infectious Disease**Title:** Public Health Reporting and National Notification for Invasive *Cronobacter* Infection Among Infants

Check this box if this position statement is an update to an existing standardized surveillance case definition and include the most recent position statement number here: N/A.

Synopsis:

- This position statement creates a standardized surveillance case definition for invasive *Cronobacter* infection among infants (less than 12 months of age) and recommends that invasive *Cronobacter* among infants be made nationally notifiable.
- A standardized case definition for invasive *Cronobacter* infection among infants is needed to estimate incidence, identify risk factors, promptly detect and trace outbreaks, and inform control and prevention measures.
- Invasive *Cronobacter* infection among infants should be nationally notifiable to facilitate heightened clinical awareness and support a coordinated response among federal agencies to an agent with the potential for multistate outbreaks.
- Case ascertainment criteria include an infant with suspicion of clinical *Cronobacter* infection or detection of *Cronobacter* spp. from a normally sterile site.
- Case classification criteria include confirmed cases, which are characterized by an invasive *Cronobacter* infection among infants from a normally sterile body site. Invasive *Cronobacter* infection among infants is most commonly characterized by sepsis and/or meningitis.
- Case classification criteria include probable cases, which are characterized by epidemiologic risk factors and supportive laboratory evidence, which may involve a non-sterile site.
- Case classification criteria also include suspect cases, which may involve a non-sterile site or epidemiological risk factors.

I. Statement of the Problem

Cronobacter spp. can cause systemic infections in neonates with a reported case fatality rate of approximately 40% (1). *Cronobacter* can be isolated from a wide range of environments indicating their ability to survive in difficult conditions, yet the relationship between these potential environmental sources and infant disease remains unclear (2). *Cronobacter* are ubiquitous in the environment and have been detected in reconstituted powdered infant formula (PIF), which is not a sterile product and has been recognized as a primary vehicle for *Cronobacter* transmission (3). Microbiological contamination of PIF can potentially occur at multiple points during production or distribution. Additionally, some *Cronobacter* infections have been traced to PIF preparation and storage by consumers in hospital and home settings (1,4,5). *Cronobacter* investigations have received national attention due to their association with infant infections and intrinsic contamination of PIF (6,7). In early 2022, in a particularly high-profile situation, the United States (U.S.) Food and Drug Administration (FDA) investigation resulted in one of the top U.S. suppliers of PIF voluntarily recalling formula manufactured at one of its plants (8,9).

The source and vehicle of transmission are not always clear in *Cronobacter* investigations. A standardized case definition for invasive *Cronobacter* infection among infants (less than 12 months of age) will facilitate the systematic surveillance of this illness and its various sequelae, enabling accurate estimates of incidence and burden of invasive disease in infants so public health authorities can determine the most effective prevention and control measures. While the addition of invasive *Cronobacter* infection among infants to the *Nationally Notifiable Conditions (NNC) List* will neither change immediate public health action taken in response to an outbreak nor directly reduce the number of illnesses and deaths associated with *Cronobacter* spp., its addition will facilitate notification at the national level, which may facilitate:

- (1) reporting changes at the state and local level, that would enable prompt detection, investigation, and response;

- (2) more accurate incidence estimates and risk factor transmission data to inform prevention;
- (3) a more comprehensive coordinated response among federal stakeholders to an agent with the potential for multistate outbreaks; and
- (4) an increase in awareness among health professionals, which is essential for prevention, early detection, timely treatment, and may increase the number of available isolates for sequencing during investigations.

II. Background and Justification

Cronobacter spp. belong to the order Enterobacteriales, which are Gram-negative bacteria (10). *Cronobacter* spp. are opportunistic pathogens linked to illnesses and outbreaks of life-threatening necrotizing enterocolitis, meningitis, and sepsis in neonates, infants, and other susceptible populations (4). In 2007-2008, the bacteria were reclassified under the genus *Cronobacter* which replaced the former single species *Enterobacter sakazakii* (4). To date, the most clinically relevant species are *C. sakazakii* and *C. malonaticus*, which are recognized as causing invasive disease in infants (4).

The incidence of invasive *Cronobacter* infection among infants in the U.S. is estimated to be 0.49 cases/100,000 infants, or approximately 19-20 cases annually, although cases are likely underreported (3,11). In 2001, the U.S. FDA investigated contamination of PIF products following a fatal infection attributed to *C. sakazakii* and use of PIF in a Tennessee hospital with one case of meningitis and eight additional cases of *C. sakazakii* colonization (7). Since 2002, the FDA has recommended only ready-to-feed liquid formula for hospitalized neonates; however, despite this recommendation, *Cronobacter* infections continue to occur in the hospital setting suggesting additional need to address infection control issues and hand hygiene, handling and storage practices, and implementation of safer alternatives to PIF (1,3). Neonates and infants are at greatest risk for high morbidity and mortality due to their immature immune systems. Other factors for high morbidity and mortality include premature delivery, pregnancy-related disease in the gestational parent, or treatment with certain drugs (12).

Cronobacter can survive in desiccated material and hospital and home environments for long periods of time. *Cronobacter* can form biofilms, which may promote antibiotic resistance and can lead to resistance to cleaning and sanitizing agents. *Cronobacter* have been associated with several neonatal intensive care unit outbreaks (10).

Although *Cronobacter* spp. have been detected in other food products, the environment, and in some infected infants that did not consume PIF, contaminated PIF has been linked to nearly all *Cronobacter* infections for which a source was found (13). Intrinsic contamination of PIF can occur at any stage of manufacturing at the factory before distribution of product for retail. Extrinsic contamination can occur once the container is opened by the user at any stage of reconstitution through contaminated water, utensils, work surfaces; at the time of feeding (e.g., using contaminated feeding bottles or enteral tubing with existing biofilm); or because of inappropriate storage conditions (e.g., poor refrigeration or storage for too long at room temperature) (3). *Cronobacter* can still be present in PIF despite FDA regulations requiring end-product testing as the pathogen may be non-homogenously distributed in the PIF due to clumping of the product (3). Given the limitations of end-product testing and the opportunity for extrinsic contamination post-production, public health surveillance is necessary (8).

Rapid and accurate pathogen identification and speciation is vital for effective public health surveillance and outbreak detection. Unlike most foodborne pathogens, *Cronobacter* infections are not required to be reported, except in Minnesota and Michigan (as of April 2023); therefore, standardized epidemiological information is not captured to inform prevention efforts, and true incidence of invasive *Cronobacter* infection among infants is unknown (8). Standardized surveillance for *Cronobacter* is necessary to help estimate incidence, identify risk factors, promptly detect and trace outbreaks, and inform control and prevention measures. Through increased awareness and submission of isolates (with the designation of invasive *Cronobacter* infection among infants as nationally notifiable), it is expected that subtyping by whole genome sequencing (WGS) or other advanced molecular methods would expand, thereby enabling more rapid and accurate species identification and cluster detection of related cases. National notification would contribute to understanding the evolving epidemiologic profile of the disease in the U.S. and lead to better attribution of the causes of contamination. This improved understanding would enable health officials to develop targeted education and prevention programs for the public and healthcare providers.

III. Statement of the Desired Action(s) to be Taken

CSTE recommends the following actions:

1. Implement a standardized surveillance case definition for **invasive *Cronobacter* infection among infants**.
 - A. Utilize standard sources (e.g., reporting*) for case ascertainment for **invasive *Cronobacter* infection**. Surveillance for **invasive *Cronobacter* infection among infants** should use the recommended sources of data to the extent of coverage presented in Section V.
 - B. Utilize standardized criteria for case ascertainment for **invasive *Cronobacter* infection among infants** presented in Section VI and Table VI in Technical Supplement.
 - C. Utilize standardized criteria for case classification for **invasive *Cronobacter* infection among infants** presented in Section VII and Table VII in Technical Supplement.
2. Utilize standardized criteria for case ascertainment and classification (based on Sections VI and VII and Technical Supplement) for **invasive *Cronobacter* infection among infants** and **add** invasive *Cronobacter* infection among infants to the *Nationally Notifiable Condition List* using the following notification** timeframe:
 - Immediately notifiable, extremely urgent (within 4 hours)
 - Immediately notifiable, urgent (within 24 hours)
 - Routinely notifiable
 - No longer notifiable
3. CSTE recommends that all States and Territories enact laws (statute or rule/regulation as appropriate) to make this disease or condition reportable in their jurisdiction. Jurisdictions (e.g., States and Territories) conducting surveillance (according to these methods) should submit case notifications** to the Centers for Disease Control and Prevention (CDC).
4. Expectations for Message Mapping Guide (MMG) development for a newly notifiable condition: the National Notifiable Diseases Surveillance System (NNDSS) can receive HL7-based messages for case notifications; the specifications for these messages are presented in MMGs. When CSTE recommends a new condition be made nationally notifiable, CDC must obtain Office of Management and Budget Paperwork Reduction Act (OMB PRA) approval prior to accepting case notifications for the new condition. Under anticipated timelines, notification using the Generic V2 MMG would support transmission of the basic demographic and epidemiologic information common to all cases and could begin with the new MMWR year following the CSTE annual conference. Input from CDC programs and CSTE would prioritize development of a disease-specific MMG for the new condition among other conditions waiting for MMG development.
5. CDC should publish data on invasive *Cronobacter* infection among infants as appropriate (see Section IX). CSTE recommends the following case statuses be included in the CDC Print Criteria:
 - Confirmed
 - Probable
 - Suspect
 - Unknown
6. CSTE recommends that all jurisdictions (e.g., States, Localities, or Territories) with legal authority should conduct public health surveillance and use the case classifications included in this standardized surveillance position statement.

* *Reporting: process of a healthcare provider, laboratory, or other entity submitting a report (case information) of a condition under public health surveillance to local, state, or territorial public health.*

***Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Conditions List to CDC.*

IV. Goals of Surveillance

To detect a source(s) of invasive *Cronobacter* infection among infants that are of public health concern (e.g., contaminated infant formula or environmental contamination in congregate settings), identify risk factors, promptly detect and trace outbreaks in order to stop transmission, and inform control measures. Standardized surveillance can enable accurate estimates of incidence and burden of invasive *Cronobacter* infection among infants and help public health authorities determine the most effective prevention and control measures.

V. Recommended Data Sources and Methods for Surveillance

Surveillance for invasive *Cronobacter* infection among infants should use the following recommended sources of data and/or methodologies and the extent of coverage listed in Table V.

CDC recommends that an isolate needing speciation for every suspected case of *Cronobacter* be sent to the Enteric Diseases Laboratory Branch, CDC (14). Culture confirmation of culture-independent diagnostic test (CIDT) positive specimens should be performed to enable further characterization via WGS. WGS offers pathways to further understand sources of *Cronobacter* infections and improve outbreak detection and traceback (5). Jurisdictions may require laboratories to submit retained isolates to appropriate federal and state public health laboratories for confirmation through WGS and bioinformatic analysis.

Table V. Recommended Sources of Data, Surveillance Methods, and Extent of Coverage for Ascertainment of Cases of invasive *Cronobacter* infection among infants.

Source of Data/Methodology for Case Ascertainment	Coverage	
	Population-Wide	Sentinel Sites
Clinician reporting	X	
Laboratory reporting	X	
Reporting by other entities, specify: hospitals, veterinarians, pharmacies, poison centers	X	
Death certificates	X	
Hospital discharge or outpatient records	X	
Data from electronic medical records	X	
Telephone or online survey		
School-based survey		
Other, specify: N/A		

VI. Criteria for Case Ascertainment

Case ascertainment is the process through which public health identifies potential cases of a disease or condition using data reported or provided to public health by healthcare, laboratories, and other reporting entities. This public health reporting is triggered by the case ascertainment criteria (a single criterion or a combination of criteria) included in this position statement, and each initial report sent to public health should include common data elements and disease-specific data elements. Case ascertainment criteria are not intended to be used for clinical diagnosis purposes.

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition and recommended reporting procedures.

Recommended reporting procedures for invasive *Cronobacter* infection among infants:

- All cases of invasive *Cronobacter* infection among infants (less than 12 months of age) should be reported according to state regulations.

- Reporting should be ongoing and routine.
- Frequency of reporting should follow the state health department's schedule.

Report any illness in an infant (less than 12 months of age) to public health authorities that meets the following:

- An infant meeting Clinical Criteria for Reporting AND Laboratory Criteria for Reporting, **OR**
- An infant meeting Vital Records Criteria for Reporting, **OR**
- An infant meeting Clinical Criteria for Reporting AND Epidemiologic Linkage Criteria for Reporting.

A1. Clinical Criteria for Reporting

- Suspicion of invasive disease (e.g., meningitis, sepsis, brain abscess, urinary tract infections, necrotizing enterocolitis, etc.) due to infection in an infant.

A2. Laboratory Criteria for Reporting

- Isolation (e.g., culture yielding an isolate) of *Cronobacter* spp. from a clinical specimen, **OR**
- Identification of *Cronobacter* spp. from a clinical specimen by a direct detection method (i.e., PCR or sequencing).

A3. Epidemiologic Linkage Criteria for Reporting

- A clinically compatible illness in an infant that shares an exposure with a confirmed or suspect case.

A4. Vital Records Criteria for Reporting

- Any infant whose death certificate lists *Cronobacter* spp. as an underlying cause of death or a significant condition contributing to death.

B. Disease-Specific Data Elements to be Included in the Initial Report

Disease-specific data elements should be included in addition to the common data elements that are to be reported for all initial individual case reports (see CSTE Position Statement 09-SI-01 “Common Core Data Elements for Case Reporting and Laboratory Result Reporting” <https://cdn.ymaws.com/www.cste.org/resource/resmgr/PS/09-SI-01.pdf>). Public health authorities do not expect that an initial report will contain all the information necessary for case investigation and case classification.

Demographics

- Hospitalization details, including admission and discharge

Clinical Information

- Date of hospitalization, if applicable
- Date of death or discharge, if applicable
- Description of clinical symptoms and signs of illness
- Previous medical history including birth history

Epidemiological Risk Factors

- Detailed feeding history during the 7 days before illness onset including:
 - Description of type(s) of infant feed
 - Description of preparation of infant feed
 - Description of cleaning of infant feeding supplies
 - Detailed infant feeding product information (e.g., product type, formulation, brand, lot number/best by date, date opened)

Laboratory/Imaging data

- Results of select imaging studies (e.g., CT, MRI, ultrasound), if performed

Comment: Jurisdictions are encouraged to utilize the CDC Cronobacter spp. case report form and consult with CDC when investigating Cronobacter case.

VII. Case Definition for Case Classification

This case definition for case classification is intended solely for public health surveillance purposes and does not recommend criteria for clinical diagnosis purposes. Once a public health agency has ascertained data on potential cases of a disease or condition from reporting entities, the public health agency assigns case statuses based on the case classifications included within this position statement.

A. Narrative: A description of criteria to determine how public health should classify a case of invasive *Cronobacter* infection among infants (less than 12 months of age).

A1. Clinical Criteria

- In the absence of a more likely alternative diagnosis, an acute illness in an infant characterized by an invasive infection, including but not limited to meningitis, cerebral abscess, sepsis, necrotizing enterocolitis, or urinary tract infection.

A2. Laboratory Criteria*

Confirmatory Laboratory Evidence:

- Isolation by culture of *Cronobacter* spp. in a clinical specimen from a normally sterile site (e.g., blood or cerebrospinal fluid).

Presumptive Laboratory Evidence: N/A

Supportive Laboratory Evidence:

- Isolation of *Cronobacter* spp. in a clinical specimen from a non-sterile site (e.g., stool or rectum, urine, skin, respiratory secretions, or broncho-alveolar lavage, etc.)**.

** Note: The categorical labels used here to stratify laboratory evidence are intended to support the standardization of case classifications for public health surveillance. The categorical labels should not be used to interpret the utility or validity of any laboratory test methodology.*

*** Whether and how public health conducts follow-up for isolation of *Cronobacter* spp. from a non-sterile site in the absence of clinical disease is at the discretion of the jurisdiction.*

A3. Epidemiologic Linkage Criteria

- Epidemiologic risk factors within 7 days prior to illness onset in an infant:
 - Consumption of powdered infant formula (PIF) implicated as the source of infection, **OR**
 - Exposure to a non-PIF product, such as breast milk, implicated as the source of infection, **OR**
 - Residing in a congregate setting (e.g., a neonatal intensive care unit [NICU]) with an active *Cronobacter* spp. outbreak.

A4. Case Classifications

Confirmed:

- Meets clinical criteria AND confirmatory laboratory evidence.

Probable:

- Meets clinical criteria AND epidemiologic linkage criteria AND supportive laboratory evidence.

Suspect:

- Meets clinical criteria AND supportive laboratory evidence, **OR**
- Meets clinical criteria AND epidemiologic linkage criteria.

B. Criteria to Distinguish a New Case of invasive *Cronobacter* infection among infants from Reports or Notifications which Should Not be Enumerated as a New Case for Surveillance

A new case should be enumerated when:

- An infant was previously reported but not enumerated as a confirmed, probable, or suspect case, but now meets the criteria for a confirmed, probable, or suspect case, **OR**

- An infant most recently enumerated as a suspect case with supportive laboratory evidence with specimen collection date for that classification within 90 days[‡] prior but now meets the confirmed case classification, **OR**
- WGS results indicate that a new positive specimen and a prior positive specimen are genetically distinct.

[‡]This time frame may be revised in future position statements if more information indicates a different period is more appropriate.

VIII. Period of Surveillance

Surveillance should be ongoing.

IX. Data Sharing/Release and Print Criteria

CSTE recommends the following case statuses* be included in the ‘case’ count released outside of the public health agency:

- Confirmed
- Probable
- Suspect
- Unknown

*Which case statuses are included in case counts constitute the “print criteria.”

Jurisdictions (e.g., States and Territories) conducting surveillance under this case definition can voluntarily submit de-identified case information to CDC, if requested and in a mutually agreed upon format.

Production of national data summaries and national data re-release for non-NNCs:

- Prior to release of national data summaries CDC should follow the CDC/ATSDR Policy on Releasing & Sharing Data, issued on April 16, 2003 and referenced in 11-SI-01 and custodians of such data should consult the CDC-CSTE Intergovernmental Data Release Guidelines Working Group report (www.cste2.org/webpdfs/drgwgreport.pdf) which contains data release guidelines and procedures for CDC programs re-releasing state, local, or territorial-provided data.
- CDC programs have a responsibility, in collaboration with states, localities, and territories, to ensure that CDC program-specific data re-release procedures meet the needs of those responsible for protecting data in the states and territories.

X. Revision History

Position Statement ID	Section of Document	Revision Description
23-ID-03	N/A	This is the first standardized surveillance position statement for invasive <i>Cronobacter</i> infection among infants.

XI. References

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Technical Supplement
Table VI. Table of criteria to determine whether a case should be reported to public health authorities.

Criterion	Invasive <i>Cronobacter</i> Infection Among Infants		
<i>Clinical Criteria for Reporting</i>			
Suspicion of invasive disease (e.g., meningitis, sepsis, brain abscess, urinary tract infections, necrotizing enterocolitis, etc.) due to infection	N		N
Infant (less than 12 months of age)	N	N	N
<i>Laboratory Criteria for Reporting</i>			
Isolation (e.g., culture yielding an isolate) of <i>Cronobacter</i> spp. from a clinical specimen	O		
Identification of <i>Cronobacter</i> spp. from a clinical specimen by a direct detection method (i.e., PCR or sequencing)	O		
<i>Epidemiologic Linkage Criteria for Reporting</i>			
A clinically compatible illness in an infant that shares an exposure with a confirmed or suspect case.			N
<i>Vital Record Criteria for Reporting</i>			
Death certificate lists <i>Cronobacter</i> spp. as an underlying cause of death or a significant condition contributing to death		N	

Notes: N = All "N" criteria in the same column are NECESSARY to report a case.

O = At least one of these "O" (ONE OR MORE) criteria in each category (categories=clinical, laboratory, epidemiologic linkage, vital records, etc.) in the same column—in conjunction with all "N" criteria in the same column—is required to report a case.

Table VII.A. Classification Table: Criteria for defining a case of invasive *Cronobacter* infection among infants.

Criterion	Confirmed	Probable	Suspect	
<i>Clinical Evidence</i>				
Meningitis	O	O	O	O
Cerebral abscess	O	O	O	O
Sepsis	O	O	O	O
Necrotizing enterocolitis	O	O	O	O
Urinary tract infection	O	O	O	O
Infant (less than 12 months of age)	N	N	N	N
Absence of more likely alternative diagnosis	N	N	N	N
<i>Laboratory Evidence</i>				
Isolation by culture of <i>Cronobacter</i> spp. in a clinical specimen from a normally sterile site (e.g., blood or cerebrospinal fluid)	N			
Isolation of <i>Cronobacter</i> spp. in a clinical specimen from a non-sterile site (e.g., stool or rectum, skin, urine, respiratory secretions, broncho-alveolar lavage)		N	N	
<i>Epidemiologic Linkage Evidence</i>				
Consumption of powdered infant formula (PIF) implicated as the source of infection within 7 days prior to illness onset		O		O
Exposure to a non-PIF product, such as breast milk, implicated as the source of infection within 7 days prior to illness onset		O		O
Residing in a congregate setting (e.g., a neonatal intensive care unit [NICU]) with an active <i>Cronobacter</i> outbreak within 7 days prior to illness onset		O		O

Notes: N = All "N" criteria in the same column are NECESSARY to classify a case.

O = At least one of these "O" (ONE OR MORE) criteria in each category (categories=clinical evidence, laboratory evidence, and epidemiologic evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case.

Table VII.B. Classification Table: Criteria to distinguish a new case of invasive *Cronobacter* infection among infants from reports or notifications which should not be enumerated as a new case for surveillance.

Criterion	Confirmed	Probable	Suspect
<i>Criteria to distinguish a new case</i>			
An infant was previously reported but not enumerated as a confirmed, probable, or suspect case, but now meets the criteria for a confirmed, probable, or suspect case	S	S	S
An infant most recently enumerated as a suspect case with supportive laboratory evidence with specimen collection date for that classification within 90 days [±] prior but now meets the confirmed case classification	S		
WGS results indicate that from a new positive specimen and a prior positive specimen from the same case are genetically distinct	S		S

Notes: S = This criterion alone is SUFFICIENT to enumerate as a new case.