Probiotic sepsis in infants under 2 years of age

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Question

What is the minimum annual number of cases of probiotic sepsis in infants under 2 years of age seen by paediatricians across Canada, and what are the associated risk factors, clinical scenarios, morbidity, and mortality?

Background

The use of probiotics in paediatric populations has gained significant attention in recent years, driven by their proposed benefits in promoting gut health, enhancing immune function, and preventing or treating various gastrointestinal disorders.[1] Probiotics, typically consisting of live micro-organisms, such as *Lactobacillus* and *Bifidobacterium* species, are increasingly incorporated into infant formulas, supplements, and therapeutic regimens for infants and children.

Despite the growing popularity of probiotics, robust evidence supporting their efficacy and safety in children remains limited.[2,3] While some studies suggest potential benefits, particularly in the prevention of antibiotic-associated diarrhea and the management of irritable bowel syndrome, the majority of clinical trials have been small-scale and heterogeneous, with varying strains, dosages, and study populations.[3,4] This lack of standardization, coupled with the relatively few large-scale randomized controlled trials, has led to inconclusive results and an ongoing debate regarding the widespread use of probiotics in paediatric care.[2-5]

Increased use of probiotics, particularly among vulnerable populations such as preterm infants and immunocompromised children, raises concerns about the risk of adverse effects, including probiotic sepsis.[6,7] While none of the randomized trials included in the systematic reviews of probiotic use in preterm infants[8,9] described probiotic sepsis, real-world cases of probiotic sepsis and mortality have been reported.[7] A systematic literature review identified 32 cases of probiotic sepsis in infants that included 7 case reports (7 preterm neonates), 8 case series (22 preterm neonates), and one cohort study (3 preterm neonates).[7] Of these cases, genomic analysis confirmed that 25 cases of sepsis were due to the administered probiotic strain.[7] Although the majority of these cases were successfully treated with antibiotics, there were two reports of neonatal deaths.[7] Recent cases of probiotic sepsis in preterm infants in Canada and the United States have prompted Health Canada and the U.S. Food and Drug Administration to issue warning letters regarding the use of probiotics in neonatal intensive care.[10,11]

The risk of probiotic sepsis is not limited to preterm infants. In a systematic review of children, D'Agostin et al. highlighted that the use of probiotics in high-risk populations, such as critically ill children, may pose significant risks.[6] In their review, specific risk factors that heighten the potential for harm included prematurity, presence of intravenous catheters, pre-existing intestinal diseases, reliance on respiratory support, and congenital heart disease.[6] Nevertheless, instances of probiotic sepsis have been reported in otherwise healthy infants with

gastroenteritis, raising concerns regarding the safety of probiotic administration in this population.[6]

Given the widespread use of over-the-counter probiotics, many parents administer them to their children, including to preterm infants after hospital discharge.[12] However, little is known about adverse events following the use of probiotics, underscoring the need for improved surveillance systems to monitor the safety of probiotics. Rigorous research is also necessary to establish clear guidelines and safety profiles, ensuring that the benefits of probiotics outweigh potential risks, particularly in vulnerable paediatric populations where the rare occurrence of probiotic-associated sepsis remains a concern.

This survey aims to provide comprehensive data on probiotic sepsis cases in infants under two years of age to inform clinical guidelines, enhance patient safety, and guide future research. The collected information could be used to develop evidence-based recommendations for safely using probiotics in infants and neonates.

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Methods

This study will utilize the established methodology of the Canadian Paediatric Surveillance Program (CPSP) to monitor probiotic sepsis in infants under 2 years of age. Approximately 2700 paediatricians and paediatric subspecialists will be surveyed monthly to report any new cases diagnosed in the preceding month. Paediatricians and subspecialists who receive the CPSP monthly case report form will receive this protocol, including the surveillance case definition below. Those who report a case will be asked to complete a detailed clinical questionnaire that includes questions on risk factors, clinical characteristics, and outcomes for all identified cases.

Case definition

Report any patient under 2 years of age (up to their 2nd birthday) meeting **ALL four** of the following criteria of probiotic sepsis:

1) Receiving a probiotic
2) Presents with systemic signs or symptoms of infection (e.g., temperature instability, apnea/bradycardia, hypotension, lethargy, or feeding intolerance)
3) Blood culture confirms the presence of one or more micro-organisms representing a probiotic strain*
4) Requires clinical intervention (e.g., initiation or escalation of antimicrobial therapy).

Exclusion criteria

- Blood culture confirming the presence of a strain of *Streptococcus* (but report ***salivarius or thermophilus)***
- Positive culture of a probiotic strain from non-sterile fluid, such as endotracheal aspirate

- Positive culture of a probiotic strain from cerebrospinal fluid, peritoneal fluid, or urine
- Probiotic bacteremia without clinical or laboratory signs of sepsis

[*] **Examples of possible probiotic strains that could cause probiotic sepsis:**
  - ***Lactobacillus:*** *rueteri, rhamnosus, acidophilus, helveticus, paracasei, delbrueckii subsp. bulgaricus, plantarum*
  - ***Bifidobacterium:*** *longum, lactis, animalis, bifidum, breve*
  - ***Streptococcus:*** *salivarius, thermophilus*
  - ***Saccharomyces:*** *boulardii*
  - ***Pediococcus:*** *pentosaceus*

The above list is not exhaustive and includes only common probiotic strains. **Report positive blood cultures for all strains of *Lactobacillus, Bifidobacterium, Saccharomyces, and Pediococcus*, as well as *Streptococcus salivarius or thermophilus.***

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Objectives

1) Estimate the minimum annual number of cases of probiotic sepsis in infants under 2 years of age
2) Determine risk factors and clinical scenarios of cases of probiotic sepsis in infants under 2 years of age
3) Determine the morbidity and mortality associated with probiotic sepsis in infants under 2 years of age

Duration

May 2026 to April 2028

Expected number of cases

Based on the literature review, it is anticipated the study will identify approximately 10–20 cases of probiotic sepsis in infants less than 2 years of age every year across Canada.

Study limitations

A limitation of this study is the reliance on voluntary reporting within the CPSP surveillance system, which may lead to the under-representation of probiotic cases in Canadian infants. Additionally, surveillance data is based on information extracted from patient charts after clinical encounters, meaning that key data elements, such as aspects of patient history, physical examination, or diagnostic assessments not routinely documented, may be missing. Paediatricians and paediatric subspecialists may be more likely to report cases that are severe or unusual, potentially overlooking milder cases of probiotic sepsis, leading to an overestimation of severity. Probiotic sepsis may be rare, resulting in a small number of cases reported, which could limit the ability to draw generalizable conclusions. Despite these limitations, the surveillance system still provides valuable clinical data that would enhance the understanding of serious cases of probiotic sepsis in Canadian infants.

Ethical approval

- University of Calgary Research Ethics Board
- Health Canada and Public Health Agency of Canada Research Ethics Board

Analysis and publication

Study data will be analyzed to provide information to healthcare practitioners and other stakeholders to better understand the risk factors of probiotic sepsis and serious and life-threatening sepsis in Canadian infants in relation to probiotics supplementation.

Given the differences between the patient populations of infants with probiotic sepsis, if possible, data will be analyzed and reported separately for the following two groups:

1) Hospitalized high-risk infants (e.g., neonatal intensive care unit [NICU] patients, NICU graduates who have never been discharged home)
2) Otherwise healthy infants (e.g., receiving probiotics in outpatient or community settings)

This stratification will apply to all analyses, including minimum incidence of probiotic sepsis, probiotic strains used, and outcomes. Where appropriate, subgroup analyses will be performed within each group to account for relevant factors such as gestational age or underlying conditions.

Knowledge translation

The results of this study will be disseminated through the following mechanisms:

- Publication in a peer-reviewed paediatric journal
- Presentations at national and international paediatric and neonatal conferences, including the Canadian Paediatric Society (CPS) Annual Conference
- Development of clinical guidelines and safety recommendations for the use of probiotics in infant and neonatal care, in collaboration with the CPS Fetus and Newborn Committee

References

1. Garcia-Santos JA, Nieto-Ruiz A, Garcia-Ricobaraza M, Cerdo T, Campoy C. Impact of probiotics on the prevention and treatment of gastrointestinal diseases in the pediatric population. *Int J Mol Sci* May 29 2023;24(11): 9427. doi:10.3390/ijms24119427
2. Martinelli M, Banderali G, Bobbio M, et al. Correction to: Probiotics' efficacy in paediatric diseases: which is the evidence? A critical review on behalf of the Italian Society of Pediatrics. *Ital J Pediatr*. Aug 17 2020;46(1):116. doi:10.1186/s13052-020-00880-x
3. Schneider R, Sant'Anna A. Using probiotics in paediatric populations. *Paediatr Child Health* Dec 2022;27(8):482–502. doi:10.1093/pch/pxac087

4. Szajewska H, Berni Canani R, Domellof M, et al. Probiotics for the management of pediatric gastrointestinal disorders: Position paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications. *Journal of pediatric gastroenterology and nutrition* Feb 1 2023;76(2):232–47. doi:10.1097/MPG.0000000000003633
5. Szajewska H. Biotics in pediatrics: Separating hype from reality. *Global Pediatrics* Mar 2024;7:100113. doi:10.1016/j.gpeds.2023.100113
6. D'Agostin M, Squillaci D, Lazzerini M, Barbi E, Wijers L, Da Lozzo P. Invasive infections associated with the use of probiotics in children: A systematic review. *Children (Basel)* Oct 16 2021;8(10):924. doi:10.3390/children8100924
7. Kulkarni T, Majarikar S, Deshmukh M, et al. Probiotic sepsis in preterm neonates-a systematic review. *Eur J Pediatr* Jun 2022;181(6):2249–62. doi:10.1007/s00431-022-04452-5
8. Sharif S, Meader N, Oddie SJ, Rojas-Reyes MX, McGuire W. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. *Cochrane Database Syst Rev*. Jul 26 2023;7(7):CD005496. doi:10.1002/14651858.CD005496.pub6
9. Wang Y, Florez ID, Morgan RL, et al. Probiotics, prebiotics, lactoferrin, and combination products for prevention of mortality and morbidity in preterm infants: A systematic review and network meta-analysis. *JAMA Pediatr* Nov 1 2023;177(11):1158–67. doi:10.1001/jamapediatrics.2023.3849
10. U.S. Food and Drug Administration (FDA). Risk of Invasive Disease in Preterm Infants Given Probiotics Formulated to Contain Live Bacteria or Yeast. 2023 Sep. [cited 2024 Feb 26]. Available from: https://www.fda.gov/media/172606/download?attachment
11. Health Canada. Use of probiotics in preterm infants. 2023 Oct. [Cited 2024 Feb 26]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/october-2023.html#a3_1a
12. Irwin N, Davis D, Currie M. Probiotic supplementation in well children: A scoping review. *Journal of Child Health Care* 2019;24(3):386–401. doi:10.1177/1367493519864750

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