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Invasive Infection Associated With Probiotics in Adults: Does the Pathogen Originate From the Product or the Host Intestine?

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Abstract

Probiotics are live microorganisms administered on an outpatient basis and in hospital settings, including intensive care units, and the genera they contain have been associated with bacteremia, fungemia, and endocarditis. The question of how frequently this occurs is often raised. This review argues that this question cannot be answered until a prior question is resolved: whether the isolated microorganism originates from the administered product. Establishing this attribution requires comparing the isolate with the strain listed in the formulation because the same genera inhabit healthy intestines, and routine identification does not distinguish one strain from another. Therefore, this review addresses whether the relationship between probiotic administration and invasive infection by the microorganism it contains is causal and to what extent it is. The outcome is operationally defined as the isolation of one of these microorganisms in the blood or another normally sterile site in a patient with compatible symptoms, excluding colonization. We organized the evidence according to the nine Bradford Hill criteria, applied at two distinct levels: whether administering the product increases the risk among those exposed and whether a specific episode stems from the administered strain. Four databases were consulted, with coverage until August 2026 and a status check in September. Neonatal and pediatric populations were excluded from the study. Among the identified evidence, the association is strongly supported by biological plausibility, coherence, and analogy and weakly supported by specificity and experimental evidence. These two weak criteria are precisely what would determine causality; therefore, the published frequencies represent a maximum, rather than an estimate. The risk is demonstrated in individual cases; however, its population-level magnitude cannot be established based on the evidence we identified.

Categories: Internal Medicine, Infectious Disease, Gastroenterology
Keywords: bacteremia, causality, critical illness, fungemia, molecular typing, patient safety, probiotics, saccharomyces boulardii

Introduction And Background

A live microorganism administered to a patient with a compromised intestinal barrier and permanent vascular access can enter the bloodstream and cause bacteremia, fungemia, or endocarditis. The genera used in probiotic preparations have done so, and that is the question this review asks: when it happens, is the organism the one that was administered? The decision at the bedside depends on an answer that routine laboratory testing cannot give.

Probiotics are live microorganisms administered to provide health benefits [1] in amounts on the order of billions of colony-forming units per dose [2]. They are based on few genera: lactobacilli, reclassified in 2020 into several new genera; *Bifidobacterium*; the yeast *Saccharomyces boulardii* (*S. boulardii*); and spore-forming bacteria such as *Alkalihalobacillus clausii* (*A. clausii*) and *Clostridium butyricum* (*C. butyricum*) [3-7]. Several are available over the counter.

Their hospital indications include the prevention of antibiotic-associated diarrhea and *Clostridioides difficile* (*C. difficile*) infection [3,8], and in critically ill patients, they have been studied as prophylaxis against nosocomial infection: in 20 trials involving 5,136 critically ill adults, they reduced ventilator-associated pneumonia (relative risk 0.69; 95% confidence interval, 0.57 to 0.84) [9], and a network meta-analysis of 55 trials involving 7,119 critically ill adults ranked synbiotics first among five compared therapies [2]. The use is not marginal: more than one-third of eligible patients in the two largest hospital cohorts received a probiotic preparation [8,10].

The obstacle to answering the safety question is not one of count but of identity. Laboratories identify these isolates at the species level, and the fact that the species of the isolate matches that of the formulation is consistent with the microorganism coming from the product, but also with it coming from the patient's own

flora, where these genera are common residents [3,4]. Both scenarios yield the same laboratory report and lead to opposite conclusions: if the microorganism comes from the product, it should be discontinued and the indication reviewed for similar patients; if it comes from the flora, the focus should be on the entry point, whether it be the catheter or the injured mucosa.

The question of frequency is therefore a causal question with two dimensions: whether administering the product increases the risk of invasive infection among those exposed, and whether a specific isolate originates from the administered strain. The second determines the first, because a rate built on cases attributed by species coincidence measures, at most, an upper bound of the actual risk. This review organizes the evidence according to the nine causality criteria originally established by Sir Austin Bradford Hill [11], which the author emphasized are not a checklist or mandatory conditions, but rather perspectives to be weighed collectively, of which only temporality is strictly indispensable [11].

We did not identify any previous synthesis that examined this association within an explicit causal framework, nor one that compiles, for the adult population, the published cases along with the exposed populations in which they occurred. This assertion is based on a limited verification: among the records retained by the screening process, we examined those whose titles identified them as reviews, and none of them addressed all nine criteria or distinguished between the two levels. We anticipate the result of this review here: the risk is demonstrated in individual cases, but its population-level magnitude cannot be established as long as strain comparisons remain rare. The restriction to adults is deliberate: baseline risk, indication, and the state of the intestinal barrier differ substantially in preterm infants.

Review

Review question and objectives

There is a single question: Is the relationship between administering a probiotic preparation and invasive infection by the microorganism it contains an association or a causal relationship, and at what level? Three objectives are derived from this question. The first is to determine what is required to attribute a specific isolate to the administered product and what method is used to achieve each level of proof. The second is to evaluate the identified evidence criterion by criterion, distinguishing in each case between the population level and episode level. The third is to synthesize this evaluation and state what the body of evidence supports and what it does not support.

What Counts as an Invasive Infection

The outcome is operational and must be defined before use, as it determines which studies are included. An invasive infection is defined as the isolation of a microorganism of the type found in probiotic preparations from blood or another normally sterile site in a patient with a compatible clinical presentation. Blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, and synovial fluid; deep tissue or the contents of an abscess; and heart valves are considered normally sterile; feces, respiratory secretions, urine, and skin or mucosal swabs are not considered sterile; isolation in any of these without invasion of a sterile site is colonization and is excluded.

This definition is ours and is not a validated external standard; the conditions discussed below derive from it. Bacteremia, fungemia, and endocarditis are not included simply because they are the most common presentations, but rather because they are the three conditions that result from applying the "sterile site" criterion to this literature: endocarditis is included because the valve is a sterile site, while conditions described in mucosal tissues or the intestinal lumen are excluded, regardless of how attributable they may be to the pathogen.

How the Evidence Is Reported

Three rules govern the rest of this text. Each estimate is reproduced as its source reports it, including the confidence interval and p-value when provided by the source, and omitting them when not. Each proportion is accompanied by the denominator used in its calculation, and when the source does not specify this, it is noted. Furthermore, it is clearly indicated at the point of use whether a figure is reported by the original study, calculated by a subsequent review, or calculated by us. Proportions based on different denominators are not comparable with one another and are not combined, a warning that is repeated in the captions of tables and figures that present figures from various studies side by side.

Methods of literature search

Search Strategy

PubMed and its Medical Literature Analysis and Retrieval System Online (MEDLINE) database, Scopus, Web of Science, and the Scientific Electronic Library Online (SciELO) were searched, combining controlled vocabulary terms with their free-text equivalents across three conceptual blocks, linked with “OR” within each block and with “AND” between blocks. Each Medical Subject Headings (MeSH) term was verified

against the official vocabulary prior to use. For exposure, the following terms were used: Probiotics, Lactobacillus, Lacticaseibacillus, Bifidobacterium, Saccharomyces, Saccharomyces boulardii, Bacillus, and Clostridium; for outcome, Bacteremia, Fungemia, Sepsis, Endocarditis, Abscess, and Meningitis; and for the risk context, "Catheter-Related Infections," "Immunocompromised Host," and "Critical Illness."

The same concepts were searched as free text in the title and abstract using the Title/Abstract field in PubMed, the title, abstract, and keyword field tags in Scopus, and Topic Search (TS) in Web of Science, along with their Spanish and Portuguese equivalents in SciELO. Two specific issues necessitated the duplication of terms: the 2020 reclassification described 23 new genera derived from the former *Lactobacillus* [12], meaning that a search string containing only one of the two names for the Gorbach-Goldin (GG) strain would miss two decades of publications, and the American and British spellings of bacteremia, fungemia, and septicemia coexist. "Translocation" was removed from the Scopus and Web of Science search strings after assessing its impact; it reduced the volume by nearly 58% without omitting any eligible articles.

No lower date limit was applied; this was a pragmatic decision by the review team and not derived from an external standard: the two publications that set the framework for comparison (the Finnish population-based surveillance study and the Roman outbreak) predated any reasonable cutoff [13,14]. This absence did not exclude any reference cited here, and the oldest among them dates from 1965. Studies in English, Spanish, or Portuguese were included. The search covered records available through August 2, 2026, and the PubMed query was rerun on September 13, 2026, as an update check, which retrieved twelve records with a later entry date; of these, three were found to be eligible and were included.

Screening, Full-Text Retrieval, and Sources

The selection of records is described step by step below, with the count at each stage and the exclusions that produced the next one. The databases returned 10,480 records: 821 in PubMed/MEDLINE, 5,800 in Scopus, 3,845 in the Web of Science, and 14 in SciELO. The combined export from the last three databases totaled 9,659 and contained 2,079 duplicates, leaving 7,580 unique records, which, together with the PubMed records, left 8,401 records to screen. An initial screening against the two core concepts of the question, an organism of interest and an invasive outcome, excluded 7,781 of these and removed the duplicates that remained across the four databases; 620 unique records were retained.

These 620 records were screened by title and abstract using explicit criteria. Cohort studies, laboratory records, incidence studies, systematic reviews, trials reporting infectious adverse events, and case series and reports were included. Studies exclusively involving neonates or pediatrics, veterinary studies, those conducted only in animals or in vitro, those reporting no infectious adverse events, those in which the isolation corresponded to colonization without invasion of a normally sterile site, and letters, editorials, comments, and errata were also excluded.

Of the 620 records, 296 were discarded. The most common reasons were off-topic subject matter without documented exposure to a probiotic in 177 records, a pediatric or neonatal reference in the title in 70, the absence of isolation from a sterile site in 55, the absence of any organism of interest in another 55, the veterinary setting in 24, and animal or in vitro study design in 19; thus, a single record could have multiple reasons for exclusion. This left 213 records for detailed evaluation and 111 whose titles provided sufficient indication but for which the abstract had to be retrieved before a decision could be made; 213 plus 111 plus 296 equals the original 620. Of these 324 retained records, 59 were sought in full text, selected by argumentative priority as described in the next section; the full text was obtained for 53 and six were not retrievable.

Thirty-eight references are cited: 32 among the full texts assessed, four added from the search after the screening round, of which three came from the September update check, and two deliberately included from outside the search, namely the article defining the causality criteria used as a framework and the report on the precedent in fecal microbiota transplantation. One of the cited references is behind a paywall, and its data were verified against its abstract rather than the full text; this is noted where it is used. The complete sequence, from the databases searched to the references cited, is shown in Figure *1*.

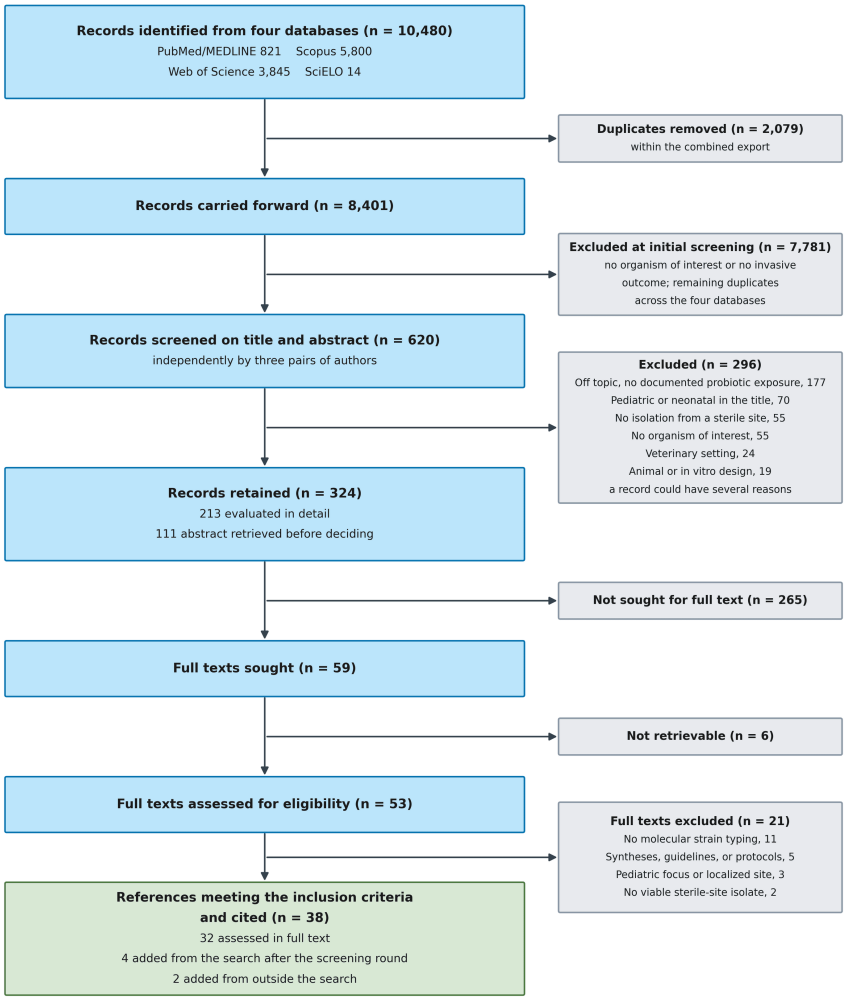


FIGURE 1: Selection of records, from the four databases searched to the references cited.

Selection of records, from the four databases searched to the references cited. The count at each stage is shown on the left and the records excluded at that stage on the right, so that each subtraction yields the following node. Of the 10,480 records identified, 2,079 duplicates were removed within the combined export from Scopus, Web of Science, and SciELO, and the remaining 8,401 were screened initially on title and abstract; the 620 that mentioned an organism of interest together with an invasive outcome were then screened independently by three pairs of authors, who resolved their discrepancies by consensus. Of the 53 full texts assessed for eligibility, 21 were excluded (reasons shown on the right) and 32 met criteria for qualitative causal synthesis; together with six additional references (four from search updates and two contextual/seminal works), 38 references are cited.

Design, Quality Assessment, and Data Extraction

This was a narrative review and was reported as such. The structured search, the explicit eligibility criteria, the paired screening, and the documented extraction were adopted to make the selection auditable, not to turn the review into a systematic one: the design remains narrative because the question posed is causal rather than quantitative, because the identified evidence is too heterogeneous for any pooled estimate, and because the synthesis is organized around a framework of causal criteria instead of around a single effect measure. No protocol was registered in advance, although the search strategy was fully documented before the searches were performed; nothing reported here is presented as compliance with PRISMA, and Figure *1* reproduces the stages of selection only so that the reader can trace them. No formal risk-of-bias or evidence-quality assessment tool was applied, and no quantitative synthesis or meta-analysis was planned or conducted. This decision stems from the heterogeneity of the identified evidence, whose populations, denominators, case definitions, and observation windows differ to such an extent that any aggregation would be incomparable.

Four characteristics were recorded for each source, and the interpretive weight assigned to it depended on these characteristics, not on whether it was included in the review: whether it was an original study or a

synthesis of other studies; whether it specified the exposed population serving as the denominator; what level on the attribution scale it reached; and whether the cited figure was the one reported by the study, one calculated by a subsequent review, or one calculated by us.

The 620 records were divided among three pairs of authors (six of the nine signatories), and both members of each pair independently reviewed them based on the title and abstract, with discrepancies resolved by consensus. The same pairs prioritized which records to review in full text and performed the data extraction, also independently within each pair and by consensus in the event of a discrepancy, and when necessary, by the decision of the principal investigator. Every quantitative statement reproduced here was verified against the full text of the corresponding report, with the exception of those already noted. The complete search strings, database field tags, and limits applied across each consulted source are detailed in the literature search summary (Table *1*).

Database	Search Term
PubMed/MEDLINE	("Probiotics"(MeSH Terms) OR "Lactobacillus"(MeSH Terms) OR "Lacticaseibacillus"(MeSH Terms) OR "Bifidobacterium"(MeSH Terms) OR "Saccharomyces"(MeSH Terms) OR "Saccharomyces boulardii"(MeSH Terms) OR "Bacillus"(MeSH Terms) OR "Clostridium"(MeSH Terms) OR "probiotic*"(tiab) OR "synbiotic*"(tiab) OR "lactobacill*"(tiab) OR "lacticaseibacillus"(tiab) OR "lactiplantibacillus"(tiab) OR "limosilactobacillus"(tiab) OR "bifidobacter*"(tiab) OR "saccharomyces"(tiab) OR "boulardii"(tiab) OR "bacillus clausii"(tiab) OR "alkalihalobacillus clausii"(tiab) OR "bacillus subtilis"(tiab) OR "clostridium butyricum"(tiab) OR "enterococcus faecium"(tiab) OR "rhamnosus GG"(tiab)) AND ("Bacteremia"(MeSH Terms) OR "Fungemia"(MeSH Terms) OR "Sepsis"(MeSH Terms) OR "Endocarditis"(MeSH Terms) OR "Abscess"(MeSH Terms) OR "Meningitis"(MeSH Terms) OR "bacteremia"(tiab) OR "bacteraemia"(tiab) OR "fungemia"(tiab) OR "fungaemia"(tiab) OR "septicemia"(tiab) OR "septicaemia"(tiab) OR "sepsis"(tiab) OR "endocarditis"(tiab) OR "bloodstream infection"(tiab) OR "blood culture"(tiab) OR "sterile site"(tiab) OR "abscess"(tiab) OR "meningitis"(tiab) OR "invasive infection"(tiab)) AND ("Catheter-Related Infections"(MeSH Terms) OR "Immunocompromised Host"(MeSH Terms) OR "Critical Illness"(MeSH Terms) OR "catheter-related"(tiab) OR "central venous catheter"(tiab) OR "immunocompromised"(tiab) OR "critically ill"(tiab) OR "intensive care"(tiab))
Scopus	TITLE-ABS-KEY("probiotic*" OR "synbiotic*" OR "lactobacill*" OR "lacticaseibacillus" OR "lactiplantibacillus" OR "limosilactobacillus" OR "bifidobacter*" OR "saccharomyces" OR "boulardii" OR "bacillus clausii" OR "alkalihalobacillus clausii" OR "bacillus subtilis" OR "clostridium butyricum" OR "enterococcus faecium" OR "rhamnosus GG") AND TITLE-ABS-KEY("bacteremia" OR "bacteraemia" OR "fungemia" OR "fungaemia" OR "septicemia" OR "septicaemia" OR "sepsis" OR "endocarditis" OR "bloodstream infection" OR "blood culture" OR "sterile site" OR "abscess" OR "meningitis" OR "invasive infection") AND TITLE-ABS-KEY("catheter-related" OR "central venous catheter" OR "immunocompromised" OR "critically ill" OR "intensive care")
Web of Science	TS=("probiotic*" OR "synbiotic*" OR "lactobacill*" OR "lacticaseibacillus" OR "lactiplantibacillus" OR "limosilactobacillus" OR "bifidobacter*" OR "saccharomyces" OR "boulardii" OR "bacillus clausii" OR "alkalihalobacillus clausii" OR "bacillus subtilis" OR "clostridium butyricum" OR "enterococcus faecium" OR "rhamnosus GG") AND TS=("bacteremia" OR "bacteraemia" OR "fungemia" OR "fungaemia" OR "septicemia" OR "septicaemia" OR "sepsis" OR "endocarditis" OR "bloodstream infection" OR "blood culture" OR "sterile site" OR "abscess" OR "meningitis" OR "invasive infection") AND TS=("catheter-related" OR "central venous catheter" OR "immunocompromised" OR "critically ill" OR "intensive care")
SciELO	("probiotico" OR "probiotic" OR "probiotico" OR "Saccharomyces boulardii" OR "Lactobacillus") AND ("bacteriemia" OR "bacteremia" OR "fungemia" OR "sepse" OR "sepsis" OR "endocarditis")

TABLE 1: Complete search strategy, by database

Field labels are shown in parentheses, for example (MeSH terms) and (tiab), because this journal reserves square brackets for citations; the database requires square brackets in those positions. The asterisk is the truncation operator. Capitalized words that are not search terms are the AND and OR operators, or field labels for each database: title, abstract, and keywords in Scopus, TS in Web of Science, and MeSH terms and tiab in PubMed/MEDLINE. The search strings for Scopus and Web of Science do not include “translocation,” which was removed after assessing its effect on the corpus already retrieved. SciELO does not handle long equations well, so the search was conducted using pairs of concepts, and the results were reviewed one by one. The counts provided in the text correspond to the August 2, 2026, search across the four databases and the September 13, 2026, PubMed update check.

The attribution scale: what would it take to bring the episode to a close

Before weighing the criteria, we must establish a standard by which the episode is evaluated. Every statement regarding the origin of an isolate falls into one of six levels, which are defined along with the method used to determine it. The scale is ordered, and each study is assigned to the highest level it achieves: a case with documented exposure and species match without typing is classified as “species-compatible,” and “documented exposure only” is reserved for cases where not even that match is recorded.

The decisive distinction lies not between high and low levels, but between methods that compare strains and those that only identify the species, which are precisely the routine methods used in clinical laboratories. An episode described using these tools cannot exceed the fourth level, regardless of how well-documented the exposure may be, and this limitation stems not from the study itself but from the method. The operational definitions and laboratory criteria corresponding to each level of this attribution hierarchy are presented below (Table 2).

Level	What has been demonstrated	Method that enables this
Confirmed strain identity	Molecular comparison between the isolate and the product strain yielded indistinguishable results	Pulsed-field gel electrophoresis, multilocus sequencing, PCR with repetitive sequences, or whole-genome sequencing
Strain identity ruled out	That same comparison was negative	The same methods, with discordant results
Inconclusive comparison	The method failed to distinguish the isolate from either the product or the commensal flora	Whole-genome sequence from a lineage that is too homogeneous, or comparison without a declared reference strain
Compatible species	The isolate belongs to the same species as the product, with no strain comparison	Biochemical identification, mass spectrometry, or 16S ribosomal RNA (rRNA) gene
Documented exposure only	Administration and subsequent isolation are documented, without an identity study	Clinical record of the prescription
Not evaluated or not reported	The study provides no data on the identity of the isolate	None

TABLE 2: Scale for attributing the isolate to the administered product

The levels are ordered from highest to lowest degree of evidence, and each study is assigned the highest level it meets.

PCR: polymerase chain reaction.

Causal evaluation according to Bradford Hill's criteria

The evidence is examined criterion by criterion, following the nine criteria described by Bradford Hill [11] and distinguishing within each one the two levels already outlined. No single criterion proves causality, and only temporality is strictly indispensable [11]. The degree of fulfillment attributed to each criterion below, and the labels used to summarize it, express a qualitative judgment reached by the authors by consensus from the evidence identified; they are not the output of a validated instrument, carry no numerical score, and another group could weigh the same evidence differently.

Strength of the association

The association is strong when measured against a concurrent comparator and disappears when measured against the general population. This discrepancy is not contradictory; it measures different things.

Compared to Concurrent Comparators

The strongest estimate comes from a registry study at five Finnish university hospitals covering slightly more than half of the country's population. It included 46 cases of *Saccharomyces cerevisiae* (*S. cerevisiae*) fungemia in adults, at least 20 of which occurred in patients who had received the probiotic, and estimated an odds ratio of 14 (95% CI 4 to 44) compared with a control group of patients with bacteremia or candidemia from the same ward and the same period, in whom exposure to the product was 5%; the 28-day mortality rate was 37%. The authors stated that they were unable to obtain microbiological evidence that the infections were caused by the strain in the product rather than by another strain [15].

The two cohorts with the cleanest reference population agreed on the order of magnitude. The first analyzed 46,729 adults hospitalized for at least 48 h, of whom 16,404 (35.1%) received at least one dose of *S. boulardii*: 18 cases of *S. cerevisiae* fungemia among those exposed (0.11%), and none among the unexposed, with incidence rates of 1.70 cases per 10,000 patient-days and 0.26 per 1,000 central venous catheter days. Admission to the intensive care unit increased the odds of the event by more than sixfold (odds ratio 6.55; 95% confidence interval, 2.28 to 18.87). The authors estimated the number needed to harm at 909 and compared this to the number needed to treat of 228 to prevent a *Clostridioides difficile* infection at their institution [8]: four infections prevented for every isolation, although the two figures do not share the same outcome, study design, or time frame.

The second study examined 56,047 adults in intensive care with central venous catheters, of whom 23,015 received probiotics: 86 catheter-associated bloodstream infections caused by an organism included in the formula, representing 0.37% of those exposed, with no cases among the 33,032 unexposed patients, placing the number needed to harm at 270. Hospital mortality was higher among patients with infection than among those exposed but without infection (25.58% vs. 13.47%); however, compared with infections caused by any other microorganism, the study found no excess attributable to the probiotic source [10]. The study design did not allow for separating the effect of the infection from that of the severity that led to both the prescription and the vascular access; the fact that the organism originated from a product did not make the bacteremia more lethal, but it did make it preventable.

Compared to the General Population

The counterbalance comes from three sources, each with a different origin. Finnish national surveillance during the expansion of consumption of the GG strain of *Lacticaseibacillus rhamnosus* (*L. rhamnosus*) recorded an average incidence of 0.29 cases of *Lactobacillus* bacteremia per 100,000 inhabitants per year, with an increase in population consumption not accompanied by an increase in incidence [13]. Two long-term surveillance studies of the same three-strain product identified no cases among 49,393 adults; however, the review that compiles them attributes this to two *C. difficile* prevention programs run by the same group, so the absence of cases was a secondary observation and not the outcome those studies were designed to measure; that review was partially funded by the manufacturer [3]. Furthermore, a hematology department that administered 2,270 doses of *S. boulardii* reported no invasive infections among its 38 colonized patients, although 89% were receiving antifungal prophylaxis or treatment at the time [16].

A Baseline Incidence for Comparison

A baseline incidence completes the picture: among 3,796 recipients of hematopoietic stem cell transplants, with no documented exposure to probiotics, 19 patients (0.5%) developed a bloodstream infection caused by one of the organisms commonly found in probiotic formulations during the first year [17], the same order of magnitude as the exposed cohorts, though in a population with a different baseline risk.

Table *3* lists the studies that reported a reference population. The unit of that reference population is not the same in all of them, so these frequencies are not comparable with one another and none of them should be read as a directly comparable estimate of risk: exposed patients, positive blood cultures, transplant recipients, and the general population are distinct denominators. Viewed in this way, the only rate based on confirmed strain identity (0.08% of the Japanese cohort [7]) is the lowest among those that recorded cases, which is consistent with the fact that higher rates include isolates that a strain comparison would have ruled out. Therefore, the strength of the association is moderate: appreciable compared to concurrent comparators, null in the population-based series, and in all cases calculated based on an attribution that the study itself did not verify.

Study	Reference population	Cases (rate)	Attribution
Wombwell et al., 2021 [8]	16,404 exposed adults	18 (0.11%)	Compatible species
Mayer et al., 2023 [10]	23,015 exposed in intensive care	86 (0.37%)	Compatible species
Sada et al., 2024 [7]	6,576 patients with positive blood cultures	5 (0.08%)	Strain identity confirmed in all 5
Sada et al., 2025 [6]	4,634 positive blood cultures	25 (0.54%)	Compatible species, with variety marker
Harmath et al., 2026 [18]	196 patients with fungal isolation	30 (15%)	Compatible species
Cohen et al., 2016 [17]	3,796 transplant recipients, with no documented exposure	19 (0.5%)	Not evaluated
Salminen et al., 2002 [13]	5.2 million residents	90 (0.29 per 100,000 per year)	Identity confirmed in 11 of 26 isolates, with no documented ingestion
Kullar et al., 2023 [3]	49,393 exposed adults	0	Not applicable
Sulik-Tyszka et al., 2018 [16]	2,270 doses; 38 colonized patients	0	Not applicable
Besselink et al., 2008 [19]	152 adults in the active arm	0 confirmed by the product	Not evaluated

TABLE 3: Studies reporting a reference population

The reference population unit was not the same across all rows, and the frequencies were not comparable with one another: four studies reported patients exposed to the product, three reported blood cultures or patients with isolates, one reported the general population, one reported colonized patients, and one (Cohen's study) reported transplant recipients with no documented exposure, included as a baseline incidence for comparison.

“N/A” indicates studies with no cases, in which there are no isolates to compare.

Table based on references [3,6-8,10,13,16-19].

The reported frequencies of invasive infection across exposed populations, categorized by the level of strain attribution achieved, are illustrated below (Figure *2*).

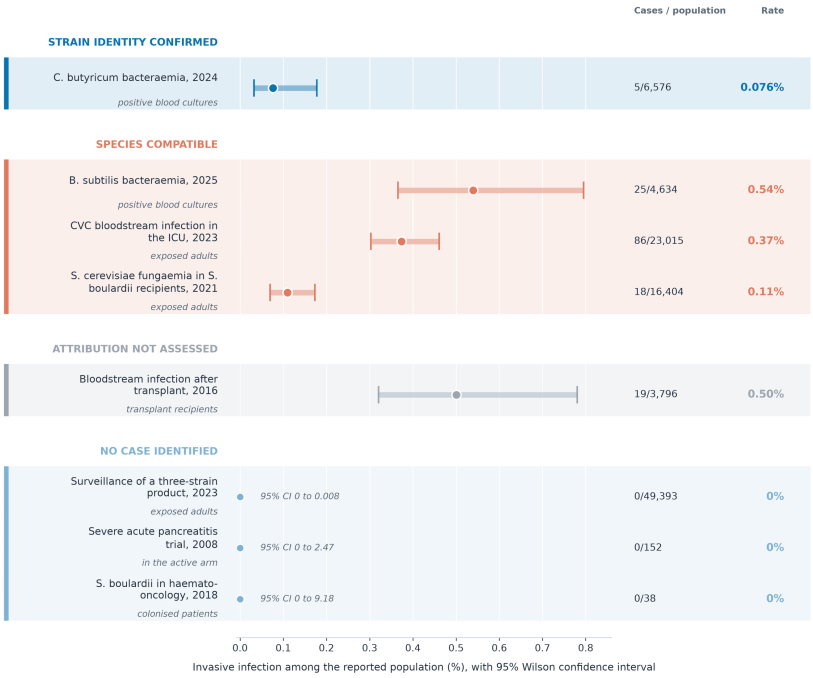


FIGURE 2: Frequency of invasive infection in adults exposed to probiotics according to the level of strain attribution.

Each line represents a study reporting its reference population, with the unit indicated on its label and observed proportion, and the 95% confidence interval calculated using the Wilson method based on published cases and population. Studies were grouped based on the extent to which the isolate originated from the product, not by the microorganism involved. Studies with no cases show their point at zero and their interval as text, so that the width of the interval does not give them a visual weight that contradicts the data. The width of this interval depends on the size of the population and not on the number of observed cases. These populations are not interchangeable, since exposed patients, transplant recipients, and positive blood cultures are distinct units; therefore, the rates are presented side by side and are not combined. Two studies in Table 3 were excluded because they lacked a population at risk to serve as a denominator: the Finnish population-based surveillance, whose unit is cases per 100,000 inhabitants per year, and the series of sterile site isolates, whose denominator consisted of patients who already had an isolate.

The figure was created using Matplotlib library (Python) based on references [3,6-8,10,16,17,19].

Consistency

Consistency Across Genres, Study Designs, and Decades

The association has been repeatedly described across different genera, healthcare settings, and decades. Among the studies we identified, cases were caused by *Lactobacillus sensu lato*, *Saccharomyces*, *Bifidobacterium*, *Bacillus*, and *Clostridium*, derived from national surveillance programs, hospital cohorts, laboratory registries, and case series, with the time span covering more than two decades [5-7,13,14,20-23]. This consistency across organisms and study designs forms the basis of the criterion.

What Varies is the Magnitude

The variation in magnitude follows a pattern. Studies that quantify exposure against a concurrent comparator find an association [8,10,15], whereas those that observe entire populations over time do not find one [3,13]. A Belgian series adds a profile that hospital cohorts do not capture: that of the very elderly patient without classic risk factors and with a prescription originating outside the hospital, in whom the case-fatality rate among those exposed was lower than among those not exposed [20]. This profile reappears in an 87-year-old man who developed septic shock with blood cultures positive for *A. clausii* after receiving the preparation for acute diarrhea, which was resolved with intensive care and daptomycin; his data were verified against the abstract, as the article is behind a paywall [24]. Endocarditis stands apart: in a review of 82 patients with infectious endocarditis caused by *Lactobacillus*, a history of probiotic consumption in the previous three months was present in 14 of the 81 cases where that data was available (17.3%), with any report that did not mention probiotics classified as “unexposed” [25].

Heterogeneity provides guidance on where to look: the association emerges when the study design compares exposed and unexposed groups within the same setting and weakens when the denominator is the general population, which is what one would expect from a rare event concentrated in a narrow hospital subgroup. The criterion was met to a moderate degree.

Specificity

This is the criterion that holds up the least and on which the others depend. The specificity that is lacking here is not that of the conclusion, which Hill already considered the weakest of his arguments, but that of the exposition itself.

The Organism is Not Unique to the Product

The same genera found in the formulations are regular residents of the healthy intestine, and the overlap is greater than the composition of the preparations suggests: *Leuconostoc*, *Pediococcus*, and *Weissella* (genera that descend from the same common ancestor as *Lactobacillus* and appear in fermented products) also cause invasive infection [26]. A review of 39 cases of invasive infection by *Weissella confusa*, in which bacteremia was the presenting symptom in 74.4% of cases and the case-fatality rate was 33.3%, concluded that evaluating probiotic safety at the species level is insufficient [27].

In the most comprehensive compilation of *Lactobacillus* bacteremia, which lists 75 individual cases between 1980 and 2023, 49 involved patients with no history of probiotic consumption [3]. A series using a genomic approach identified 15 cases of *Bifidobacterium* bacteremia, 11 in adults, none with documented exposure, and the authors were unable to trace consumption through diet or supplementation in the majority of cases [5]. In *Lactobacillus endocarditis*, the dominant predisposing factor was neither immunosuppression nor critical care, but rather dental pathology, present in 34 of the 82 patients (41.5%) [25], which points to a distinct oral entry route rather than the administered product. In a series of 196 patients with *S. cerevisiae* isolated from any sample, 30 cases involved sterile-site infection, and only nine of those 30 had prior exposure to the probiotic [18].

What the Laboratory Cannot Determine

S. boulardii cannot be distinguished from *S. cerevisiae* using these methods, including mass spectrometry, and is currently considered a subtype of *S. cerevisiae* [16,28]. Thus, an undetermined proportion of cases labeled as *S. cerevisiae* without prior exposure could correspond to the unrecognized probiotic variant, and vice versa. Biochemical identification correctly classifies only a minority of lactobacilli, and the isolated 16S ribosomal RNA gene may assign the highest score to the wrong species [29]. The division of the former genus causes the same organism to appear under two different names depending on the publication date [12]. In the case of *Weissella*, intrinsic resistance to vancomycin and phenotypic similarity to other lactic acid bacteria also lead to misidentification and delays in treatment [27].

When a Strain Comparison Was Performed

Of the 75 cases tabulated, 23 were linked to a strain identical to that of the consumed probiotic, but by age, most were preterm infants and pediatric patients, and only two were unequivocally adults; this is our own tally based on the age column of their individual data, which the article does not break down. The same source provides a counterexample: in three cases, the comparison showed that the isolate was not the same as that in the product [3], and in a 69-year-old man receiving fermented milk via a feeding tube, two laboratories conducting a blind test (one of which was the manufacturer's) found a 97.1% homology compared to the a priori threshold of 98.5% [30].

Even the most discriminatory method may prove insufficient. A study that reconstructed the global population structure of *L. rhamnosus* based on 602 sequences failed to distinguish the isolate from an 83-year-old man with prosthetic endocarditis from that of a commercial yogurt or from gut commensals: a single nucleotide variant out of more than 2.9 million aligned bases [31]. However, the same method resolved a subsequent Finnish study: it sequenced the whole genomes of 16 blood culture isolates and found none corresponding to the GG strain, even though the closest lineage reached 99.98% similarity [32].

Such comparisons were rarely attempted, and some of what is presented as one does not qualify. Of 48 cases published between 2019 and 2021, the 16S gene was sequenced in six (a species-level method) and the whole genome in two, without specifying against which strain [33]. In the best-documented series of endocarditis cases, out of 10 cases, only two achieved confirmed identity; in one case, the comparison ruled out the product, and six did not include any comparison at all [34]. A review of 92 cases caused by *Saccharomyces* attributed 37 to *S. boulardii*, with molecular species identification in 23; this was aimed at confirming the pathogen rather than comparing it to the product strain [35]. Nor did the two registry series with the most detailed clinical characterization [15,20] or the two studies with the best reference populations, which attribute cases based on nominal coincidence [8,10], perform typing.

A recent hospital series shows how far an explicit effort still falls short. It included 16 patients with *C. butyricum* isolated from blood cultures over a 10-year period, with a mean age of 37 years and central venous catheters in 75% of cases, and characterized the preserved isolates using mass spectrometry and ribotyping: all were found to belong to ribotype B, but the authors stated that this ribotyping was not used as evidence to attribute the strain to the commercial product and that strain-level attribution was not possible [36].

The Japanese *Bacillus subtilis* cohort defines the criterion from the other end. It applied a marker specific to the natto variety of the fermented food, absent in laboratory and environmental strains; 99% of the 70 isolates carried it, even though no patient reported consuming natto [6]. The marker places the isolate above the species level and below the strain level, but there was no administered product with which to compare it.

Cases With Confirmed Strain Identity in Adults

By compiling the scattered cases, we can construct a tally that no single source provides separately, using two criteria: adult patients and strain identity confirmed in the primary report we were able to read, rather than in a compilation that merely references it. We identified at least 11 episodes: two from the *Lactobacillus* compilation [3], one patient with multiple trauma [21], two intensive care patients linked by electrophoresis [22], five from the Japanese *C. butyricum* cohort [7], and one 85-year-old postoperative patient linked to the administered capsules by whole-genome sequencing [37]. This is a minimum count, not a total, since the review on endocarditis reports one additional adult case whose primary report we were unable to retrieve [34]. Eleven episodes over four decades do not allow for an estimate of frequency, but they establish that the phenomenon occurs and can be demonstrated when someone sets out to do so. The criterion is met to a limited extent

Temporality

This is the only criterion that Hill considered indispensable [11], and it is satisfied wherever exposure is recorded.

Where Exposure is Documented

The clearest evidence comes from an immunocompetent patient with multiple trauma who received *L. rhamnosus* GG via a feeding tube while she had a central venous catheter in place. She was 56 years old, and whole-genome sequencing found no single-nucleotide differences between the blood isolate and the sequence of the strain deposited by the manufacturer, compared to a maximum of 13 differences among the other genomes of that same strain included in the phylogenetic tree [21]. Similarly, an 85-year-old man was linked to the product by culturing the container he was taking [37], and in the Japanese cohort, four of the five patients with confirmed identities were receiving it at the time of diagnosis [7].

Where Verification is not Possible

Apart from these instances, the sequence can rarely be verified because exposure is poorly recorded. The *Bifidobacterium* series was unable to track consumption in most of its patients [5], and the endocarditis review classified any report that did not mention probiotics as "unexposed," a criterion that, by design, underestimates exposure [25]. Conversely, of the 37 patients attributed to *S. boulardii* in a classic review, five were not taking the product at the time of diagnosis [35].

An outbreak in a Roman intensive care unit necessitates a more precise definition of the criteria. In this case, the packet of freeze-dried yeast was opened next to a sink located 3 m from the nearest bed, and three patients who had never received the product developed fungemia; in one of them, clonal identity was confirmed against the packet stored in the pharmacy [14]. With regard to administration, there is no temporal sequence to evaluate; with regard to the product as the source, this has been demonstrated. What precedes the infection is not always administration to the patient, but rather the presence of the product in the unit. The criterion is met to a moderate to high degree where exposure is documented, and cannot be verified in most of the corpus.

Biological gradient

We did not identify any study that quantified the dose-risk relationship; therefore, the criterion can only be assessed through estimates of inoculum size, and this absence represents a lack of identified evidence rather than proof that such a study does not exist. The most direct estimate comes from the intensive care unit cohort: powdered formulations were associated with more than twice as many infections as non-powdered formulations (0.76% vs. 0.33%; odds ratio 2.03; 95% confidence interval, 1.05 to 3.95) [10]. This study compared formulation types rather than locations or reconstitution techniques; therefore, it allows for interpretations other than inoculation, including cross-contamination during handling.

The second approach is spatial and stems from the previously described outbreak in Rome, where unexposed cases appeared in beds adjacent to the point of handling [14]. The third is the magnitude of the dose itself,

on the order of billions of colony-forming units [2]. None of the three constitutes a measured dose-response relationship. The hypothesis was suggested but not confirmed.

Biological plausibility

The mechanism requires no additional hypotheses: billions of live organisms are administered per dose [2], and in the cohorts reviewed, this preparation was administered to patients with a compromised intestinal barrier and permanent vascular access.

Intestinal translocation requires a mucosa altered by mucositis, ischemia, surgery, or enteral nutrition, and this route is consistent with the profile of factors that the systematic review of *Saccharomyces* fungemia found to be associated with the exposed group: intensive care unit stay, parenteral or enteral nutrition, gastrointestinal disease with diarrhea, diabetes, and mechanical ventilation [4]. Contamination of the central venous catheter during product handling explains why the cohort that documented 86 infections did so specifically among catheter-carriers [10] and why one of the incidence rates in the study was expressed in terms of catheter days [8]. Airborne dispersion of the lyophilized preparation upon opening the package was demonstrated in the Rome outbreak [14]. The oral route of entry predominated in the endocarditis series, where dental pathology was the most common predisposing factor [25].

All four routes are documented by direct observations, and one of them involves clonal identity with the source. This criterion was strongly met. The four documented anatomical and procedural routes by which administered microorganisms reach the bloodstream in hospitalized adults are illustrated below (Figure *3*).

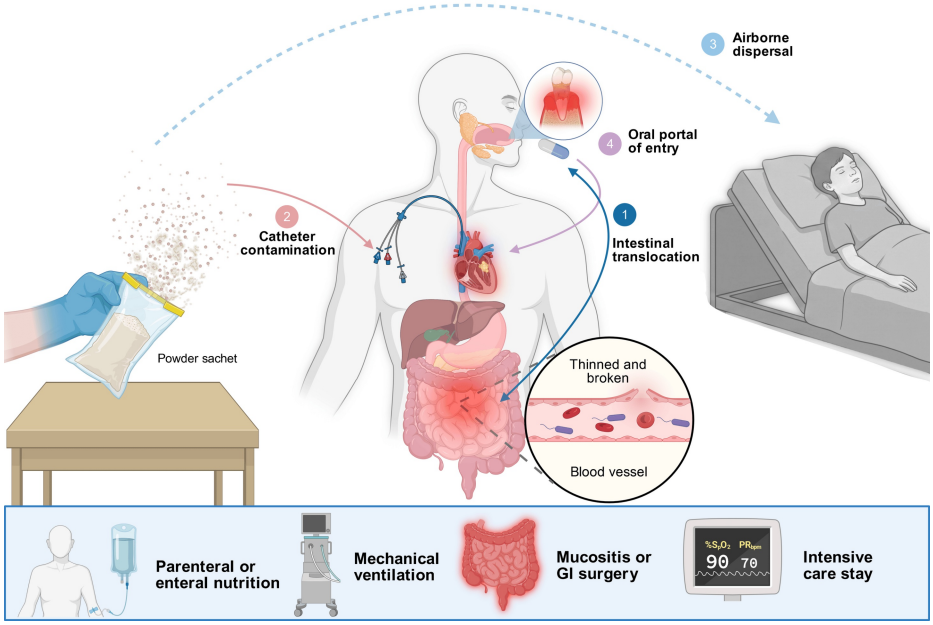


FIGURE 3: Described routes by which a microorganism contained in a probiotic preparation can reach the bloodstream in hospitalized adults.

Intestinal translocation, route 1, requires a mucosal barrier compromised by mucositis, ischemia, surgery, or enteral nutrition. Contamination of the central venous catheter during product handling, route 2, was more frequent with powdered formulations, which were associated with twice as many infections as non-powdered formulations. Airborne dispersion of the lyophilized preparation upon opening the package, route 3, reached patients who had never received it and were occupying neighboring beds, with demonstrated clonal identity compared to the packet stored in the unit. The oral route of entry, route 4, predominated in the reviewed endocarditis series, where dental pathology was the most common predisposing factor, present in 41.5% of patients. The bottom section lists the host factors that occurred most frequently in the reviewed series.

The figure was created manually using BioRender's icon library by JD Urrea Ospina (https://BioRender.com/575u6so), based on references [4,6,8,10,14,25].

Coherence

The Host Profile

The causal explanation does not require revising anything already known about bacteremia in hospitalized patients. The contributing factors are the same as those governing any catheter-associated bacteremia and

appear consistently in the reviewed series: vascular access [8,10], also present in 75% of a hospital series of *C. butyricum* bacteremia [36], severity as measured by admission to the intensive care unit [8], and the integrity of the intestinal barrier [4]. In the classic review of invasive *Saccharomyces* infection, the use of an intravenous catheter (present in 47 patients) and prior antibiotic therapy (present in 45 patients) were the most common predisposing factors [35].

What the Evidence Compels Us to Correct

The identified evidence corrects a different notion: that these episodes occur only in critically ill, immunocompromised patients. A study on the incidence of *S. cerevisiae* fungemia found no formal immunosuppression in any of its 18 cases and identified the risk factors as admission to the intensive care unit, prolonged hospital stay, and catheter use [8]. In the Japanese cohort of *Bacillus subtilis* (*B. subtilis*) bacteremia caused by the fermented food variant, 92% of cases were community-acquired, the median Pitt bacteremia score was 0, and only 20% of patients were immunocompromised [6]. The best-documented episode in the entire body of literature occurred in a patient who was explicitly immunocompetent [21]. A series of four adults with *A. clausii* bacteremia following consumption of an over-the-counter product described an intermediate profile, with a median age of 71 years, advanced comorbidities, and three deaths out of the four [23].

The resulting picture is consistent with an inoculum-and-barrier mechanism rather than one requiring immunosuppression. The systematic review of fungemia that compared the profiles of exposed and unexposed individuals and found them to differ [4] further supports the notion that exposure selects a specific type of patient rather than merely labeling the same group. This criterion was strongly met.

Experimental evidence

The Outcome That the Trials Did Not Measure

This is the second criterion that does not hold up, not because the experiments yielded negative results, but because they did not measure the outcome. The network meta-analysis of 55 trials and 7,119 critically ill adults did not report any microbiological safety outcomes, and the possibility of infection by the administered organism was mentioned once in the introduction and did not reappear thereafter [2]. The meta-analysis on ventilator-associated pneumonia, involving 5,136 randomized adults, reported bacteremia rates only in its supplementary material [9]. Therefore, there is a randomized population of thousands of adults in which this outcome was either not measured or was measured but not reported; thus, the absence of cases is not evidence of the absence of risk.

The Only Trial Showing Excess Mortality

This trial warrants careful scrutiny, as the most widely cited interpretation attributes the findings to infection. In 296 adults with anticipated severe acute pancreatitis, prophylaxis did not alter the incidence of infectious complications (30% vs. 28%; relative risk 1.06; 95% confidence interval, 0.75 to 1.51), but it was associated with excess mortality (16% vs. 6%; relative risk 2.53; 95% confidence interval, 1.22 to 5.25). This excess was attributed to non-occlusive intestinal ischemia, which occurred in nine patients in the active-treatment arm and in none in the placebo arm (a non-infectious mechanism), and the authors state that no infection was confirmed to be caused by the administered strains, although they do not describe any typing method to support that statement [19]. This trial provides evidence of harm in a specific population and through a specific mechanism, but not that this harm was due to invasive infection.

The observation closest to an experimental trial that we identified was not designed as a trial. In the Rome outbreak, pulsed-field gel electrophoresis linked the isolates to the envelope stored at the pharmacy, thereby establishing the source without randomization [14]. This was a single, unreplicated observation and does not substitute for a trial incorporating this outcome. This criterion was met to a limited extent.

Analogy

The most informative precedent does not come from probiotics but from another therapy involving live microorganisms. Two patients developed bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli following fecal microbiota transplantation in two separate clinical trials, and genomic sequencing linked both cases to the same stool donor; one of the patients died [38]. The analogy matches the three elements that matter: preparation of live organisms administered for therapeutic purposes, an invasive event caused by an organism present in it, and a vulnerable recipient population. It differs on a fourth point: in that case, the attribution was resolved, and it was resolved using a method that the probiotics literature rarely applies.

The second analogy is direct. Any organism that reaches a central venous catheter can cause bacteremia, and there is no microbiological reason why *Lactobacillus* or yeast should be exempt from this route when the product is handled near the vascular access site. The criterion is strongly met.

Summary: integrated causal assessment

Taken together, the profile of the nine criteria supports an asymmetric conclusion: causality has been demonstrated in selected individual episodes with strain-level confirmation, because at least 11 episodes in adults complete the entire chain between the administered product and the isolate [3,7,21,22,37], while attribution remains uncertain in most reported cases; at the population level, the association is real, but its magnitude cannot be estimated.

There is a precise explanation for this asymmetry. The two criteria that are least met (specificity and experimental evidence) are the ones that would resolve the attribution: the former because the organism is not exclusive to the product, and the latter because trials that randomize exposure do not measure this outcome. As long as both criteria are unmet, any published rate relies on species overlap and represents an upper bound of the actual risk. The fact that an independent review of another genus within the same family concludes that the safety assessment must move from the species level to the strain level [27] indicates that the problem is not unique to the genera reviewed here.

It is important to distinguish between two statements that are often conflated in everyday language: that the product is the source of the organism and that its administration to the patient is the route of entry. These are distinct propositions, and the choice of effective preventive measures depends on this distinction. An integrated synthesis evaluating the fulfillment of each of the nine Bradford Hill causality criteria across the available evidence is summarized below (Table *4*).

Criterion	Degree of fulfillment	Why
Strength of the association	Moderate	A noticeable association compared to competing comparators but none compared to the general population; all rates were calculated based on an attribution that the study itself did not verify
Consistency	Moderate	Studies replicated across five genres, four study designs, and more than two decades; the magnitude varies depending on whether or not a concurrent comparator is present
Specificity	Low	These genera are common intestinal residents; a large proportion of published cases have no history of consumption, and routine methods do not distinguish the probiotic variant from the commensal
Temporality	Moderate to high	Documented exposure prior to isolation in cases with confirmed identity; not verifiable where exposure records are missing
Biological gradient	Suggested, unconfirmed	Three approaches to the inoculum, none of which involves dose-risk titration
Biological plausibility	High	Four documented routes of entry with direct observations, one of which involves clonal identity matching the source
Coherence	High	The host profile matches that of any catheter-associated bacteremia, without requiring immunosuppression
Experimental evidence	Low	None of the randomized trials identified measured this outcome; the only one reporting excess mortality attributed it to non-occlusive intestinal ischemia
Analogy	High	Fecal microbiota transplantation resulted in donor-related bacteremia as determined by genomic sequencing, with the cause definitively established

TABLE 4: Integrated evaluation of Bradford Hill's causality criteria

The level of compliance summarizes the evidence reviewed in the previous sections, which includes the figures and citations supporting it; it is a qualitative and ordinal scale that expresses the authors' judgment regarding the identified evidence, and is not a quantitative score or a validated instrument.

Prepared by the authors based on the evidence reviewed in this section and the original criteria [11].

The resulting degree of compliance for each criterion, categorized into a qualitative traffic-light framework, is depicted below (Figure *4*).

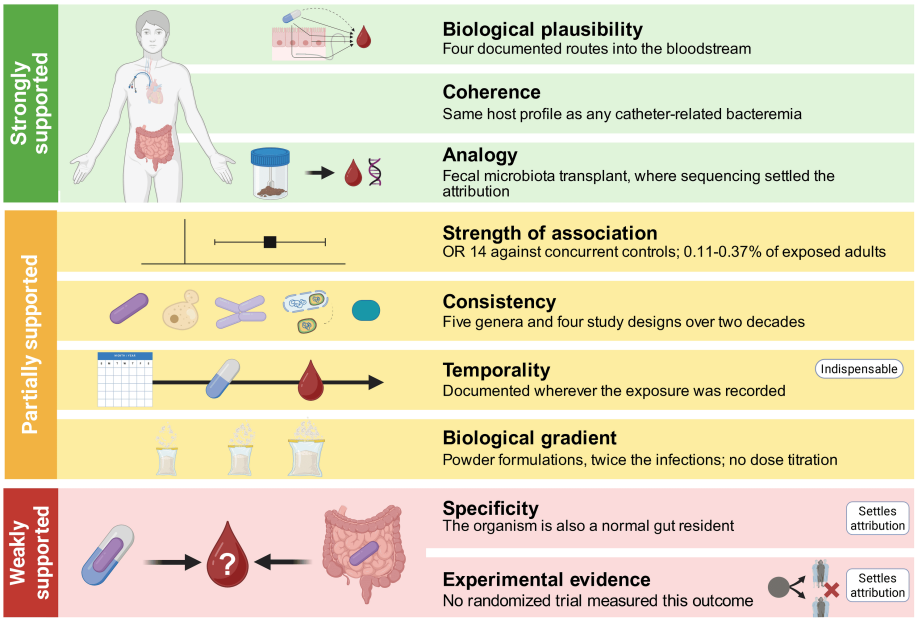


FIGURE 4: Evidence traffic light: Degree of compliance with Bradford Hill's nine causality criteria for invasive infection by the administered microorganism in adults receiving probiotics.

Each criterion is represented by a color corresponding to its degree of fulfillment based on the evidence reviewed: green, strongly supported criterion (biological plausibility, coherence, and analogy); yellow, partially supported criterion (strength of association, consistency, temporality, and biological gradient); red, weakly supported criterion (specificity and experimental evidence). Temporality is marked as indispensable because it is the only criterion that Hill considers strictly necessary. The scale is qualitative and ordinal, and the details supporting each color are presented in Table 4.

The figure was created manually using BioRender's icon library by JD Urrea Ospina based on the evidence examined in this section and the original criteria.

Where the risk is concentrated and what makes it preventable

Of the factors described, three pertained to the patient and one to the handling of the product, and this distinction has practical implications. The first three (the catheter, severity of the underlying condition, and compromised barrier) define who is at the highest risk when receiving the product, and these risks can only be addressed by restricting the indication or withdrawing it when the risk-benefit balance shifts.

The fourth factor does not depend on the patient, and the outbreak in Rome demonstrates this: the three patients who became ill without having received the product were excluded from any calculation of incidence among those exposed, and that is precisely why they are significant, because they represent harm that no calculated incidence rate among those exposed can capture [14]. The route of entry remains the affected patient's vascular access; what changes is the origin of the inoculum, which comes from the point of handling.

The implication, supported by this clonal identity rather than by an association with powdered formulations, is that part of the risk is not eliminated by restricting the indication, but rather by changing where and how the preparation is reconstituted and by separating this handling from catheter care. This is the only measure discussed that does not require sacrificing the benefit. Its basis, however, is a single documented outbreak and the comparison between formulations in one cohort, not population-level evidence of contamination: it is a precaution proportional to that evidence, and the reduction in risk that it would achieve has not been quantified.

Limitations

Scope of the Search and Framework

This review describes the evidence that the strategy made it possible to identify not all existing evidence: by design, it excludes literature not indexed in the databases consulted, published in journals with local circulation, and unpublished material. Therefore, no assertion is made regarding the absence of evidence in

absolute terms, but rather regarding the absence of evidence identified using this strategy from these sources as of this date.

The causal framework imposes its own limits. Hill's criteria were formulated for environmental exposures and chronic diseases in populations, and here they are applied to an acute adverse event whose attribution is determined on a case-by-case basis; the weight assigned to each criterion is a qualitative judgment by the authors, not the result of a validated instrument. The operational definition of the outcome is also our own; therefore, a study that would have classified an isolation in a non-sterile setting as invasive is excluded from this synthesis even if it describes the same phenomenon.

What Limits the Interpretation of the Figures

Four limitations affect these figures. Case counts are subject to publication bias in two directions that do not cancel each other out: a case in a patient taking probiotics is more likely to be published than one without that exposure, whereas institutional series with no cases are less likely to be published. Exposure was poorly recorded in a large proportion of the identified studies. Furthermore, the two characteristics that would make a rate interpretable (knowing how many patients were affected and demonstrating that the isolate came from the product) almost never coincide in the same study among those we identified; the Japanese exception [7] shows that this combination is possible. To these is added a fourth: no formal evidence-quality or risk-of-bias instrument was applied to the included studies, so the interpretive weight given to each one rests on the four characteristics recorded during extraction and on the authors' judgment, and not on a structured appraisal; a reader who wishes to weigh them differently has the design, the denominator, and the level of attribution of each study stated alongside it.

The limitations of the scope, rather than the method, deserve separate mention. This review describes only one side of the equation: the same studies in which we document the gap in safety measurement are the ones that report the benefits summarized in the introduction [2,9]. No clinical decision can be made based on only half of the evidence presented here. Finally, the restriction to the adult population implies that these conclusions are not transferable to preterm infants.

Conclusions

Causality in the relationship between the administration of probiotics and invasive infection by the microorganisms they contain has been demonstrated in selected individual episodes with strain-level confirmation, while attribution remains uncertain in most reported cases, and its magnitude at the population level is unknown. The criteria of biological plausibility, coherence, and analogy strongly support this relationship, and temporality, the only indispensable criterion, was met wherever exposure was recorded. The two criteria that are not met (specificity and experimental evidence) are precisely those that would allow us to move from an upper limit to an estimate, because the isolated organism is not exclusive to the product, and randomized controlled trials (RCTs) have not measured this outcome. Therefore, the published frequencies describe an upper limit of risk rather than the actual value.

It is clearly defined where that risk is concentrated and what makes it preventable: the critically ill patient with a central venous catheter and a compromised intestinal barrier, and a portion of the risk that does not depend on who the product is administered to, but rather on where and how it is reconstituted. The implication is not to withdraw probiotics, whose benefits this review did not evaluate, but to close the gap that prevents the measurement of their harm: comparing the isolate with the administered strain before attributing an origin to it, and incorporating infection by the administered organism into the safety outcomes of the trials studying it. This standard of proof is not unattainable; it has already been applied in other therapies based on live microorganisms.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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