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REVIEW ARTICLE

A Safe Microbe No More? Emerging Antibiotic Resistance in Probiotic *Bacillus subtilis*

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ABSTRACT

Bacillus subtilis is a GRAS-type spore-forming bacterium that is prevalent in nature and gaining popularity in the probiotic supplementation. Although the one is non-pathogenic, recent research reports show alarming signs of antibiotic resistance (AR) features that can pose a risk to human health in terms of direct infection, environmental permanence, and horizontal gene transfer (HGT) to pathogens. This is a review that summarizes existing information on the AR mechanisms in B. subtilis, its transmission patterns, clinical significance, and regulation. We posit that its spores and unregulated use of probiotics make the bacteria a silent perpetrator in the worldwide antimicrobial resistance (AMR) epidemic. There is an urgent need to have an interdisciplinary cooperation across many fields, including microbiology, clinical practice, and policy, to reduce risks.

1. Introduction

Bacterial Paradox of a Safe Bacterium Bacillus occurs in soil, water, and air and it has forms known as endospores, addressing extreme conditions in the environment. [4,6]. Its widespread use is supported by being GRAS in: Probiotics: (e.g. Enterogermina, BioSporin) intestinal flora Agriculture: (biocontrol agents) Industry: (manufacture of enzymes) [1,2,5,10].

Nonetheless, the acquisition of AR is rapid as a result of genomic plasticity. Though cases of human infection are few (0.1 percent Bacillus infections), immunocompromised people are exposed to the risk of bacteremia, endocarditis, and pneumonia. Nexus of spore fidelity, HGT aptitudes, and probiotic growth necessitate investigation [2,3,7]

2. Materials and Methods

2.1. Intrinsic Resistance

2.2. Acquired Resistance

Mobile Genetic Elements (MGEs)

Plasmids (e.g., pBS72 carrying erm, tetL) Transposons (Tn 1546-like elements with vanA) [9].

Table 1: Intrinsic Resistance of Bacteria

Mechanism	Function	Antibiotic class Affected
Spore Structure	Keratin-like coat, SASPs, low hydration	Blocks penetration of β-lactams, aminoglycosides
Efflux Pumps	Bmr, Blt (MFS transporters	Fluoroquinolones, tetracyclines
Biofilm Formation	Extracellular matrix barrier	Vancomycin, cephalosporins

Chromosomal Mutations

rpoB (rifampicin), gyrA (ciprofloxacin) [2].

Natural Competence

Uptakes environmental DNA (e.g., ARGs from Enterococcus) [3].

3. Human Health Implications

From Gut to Clinic

3.1. Probiotics: A Double-Edged Sword

30% of commercial B. subtilis probiotics harbor ARGs (e.g., tetAP, ermC) [1.2].

Documented Risks

HGT to Clostridioides difficile and Staphylococcus aureus in the gut models Long-term colonization of immunocompromised patients Regulatory Gaps: No standard to screen ARG in probiotics at international level [3,9,8,5].

3.3. Beyond the Individual: Public Health and Socio-Economic Implications

Antibiotic-resistant Bacillus subtilis is not only a microbiological curiosity but also a potential driver of wider public health challenges. In recent years, the unregulated sale and consumption of over-the-counter probiotic supplements, particularly in low- and middle-income countries (LMICs), has been identified as a possible route for the dissemination of antimicrobial resistance genes (ARGs) within community and hospital environments [11,12]. These products are often marketed to vulnerable populations, such as infants, elderly individuals, and immunocompromised patients, without undergoing standardized ARG screening prior to market release [13,14].

Once released into the environment, ARG-harboring B. subtilis strains can persist in wastewater, agricultural soils, and the food chain, providing opportunities for horizontal gene transfer (HGT) to other microorganisms [12,15]. This cycle of environmental contamination and re-entry into human populations aligns closely with the One Health framework, which emphasizes the interconnection between human, animal, and environmental health in the context of antimicrobial resistance (AMR) [16].

The economic impact of AMR is severe. Global models project that by 2050, AMR could lead to an annual loss of nearly US $2 trillion, accompanied by a significant reduction in gross domestic product (GDP) across both high- and low-income nations [17]. In LMICs, healthcare expenditures for the treatment of drug-resistant infections could increase by more than 25%, placing additional strain on already limited healthcare resources [18].

Technological solutions, including whole-genome sequencing (WGS) and machine learning-assisted genomic analysis, offer the potential to detect ARGs in probiotic strains before distribution [19,20]. However, these innovations remain unevenly implemented, with resource-constrained regions often lacking the infrastructure for routine genomic surveillance [14,19]. Coordinated international efforts are needed to establish harmonized laboratory protocols, shared genomic databases, and universal ARG testing standards for all commercial probiotic products [16].

Table 2: Infections in Vulnerable Populations

Case type	Antibiotic Resistance Observed	Clinical Outcome
Bacteremia	Ciprofloxacin	Treatment failure 20%
Pneumonia	β-lactams, macrolides	Prolonged hospitalization

4. Transmission Dynamics: A One Health Challenge:

4.1. Environmental Persistence

Spores are UV, heat and disinfectant resistant, and survive: Farming soils (manure filled with antibiotics) Food chain (fermented products, uncooked vegetables) The surfaces of the hospital (ICU surfaces) [6].

4.2. Gene Transfer Hotspots

Human Cellulose Gut: Spores germinate/comsanitize with ARGs including with commensalism via: Conjugation (pLS20 -plasmid).

Transformation (competence-induced uptake of DNA)

Wastewater: ARG in treatment water [3,9,6].

5. Regulatory and Research Challenges

5.1. Policy Shortcomings

FDA/EFSA: Have strain-specific AR profiling, but GRAS strains exempt from it. Diagnostics: B. subtilis as nothing in the clinical lab, ignoring the AR surveillance [5,10,2].

5.2. Critical Research Gaps

Risk Quantification: Probiotic-pathogen HGT events in vivo.

Toning down: Probiotic vs. environment isolates. Probiotic Engineering: liver, CRISPR-Cas deletion of ARGs in commercial strains [3,1,7].

6. Mitigation Strategies: A Roadmap

1. Enhanced Surveillance

Mandatory AR screening for all probiotic strains (incl. spore-formers). Environmental monitoring of Bacillus in One Health networks [5,6,].

Technological Solutions

Probiotics with locked ARG-free genomes. Phage-based spore disruption in clinical settings [7,4].

Global Policy Action

Unified AMR guidelines for probiotics (WHO/FAO). Public education on probiotic risks during antibiotic therapy [1,5].

7. Conclusion

An example of these harmful AMR latent in harmless microbes is Bacillus subtilis. Its spore robustness, genetic dexterity, and probiotics ubiquity form avenues of resistance transmission. in order to prevent an invisible epidemic, what we suggest [1,2,3,6].

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