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An Insight into The Streptococcus Agalactiae-Associated Stillbirth and the Potential of Probiotics as An Alternative Therapeutic Approach

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Abstract

The large number of stillbirths caused by streptococcus agalactiae globally is a matter of great public health concern, particularly in areas that have poorly developed healthcare systems. This article examines the condition of stillbirth associated with Streptococcus agalactiae. It addresses therapeutic possibilities, microbiological features, treatment issues, and epidemiological data. The review underpins the necessity for new therapies considering antibiotic resistance and probes into bacteriocins derived from vaginal microbiota. Clinical data support their ability to reduce GBS colonization and arrest vertical transmission. Therefore, more research and clinical trials are needed to validate and maximize bacteriocin use. Collaboration across countries is essential if this innovative therapeutic approach is to be implemented widely for improved maternal and neonatal health outcomes.

Keywords: Stillbirth, probiotics, Streptococcus agalactiae, Bacteriocins.

Introduction

Stillbirth is a devastating event that affects families worldwide and has significant social, emotional, and economic implications. According to [1] - A baby who dies after 28 weeks of pregnancy, but before or during birth, is classified as a stillbirth. There are nearly 2 million stillbirths every year – one every 16 seconds. Over 40% of all stillbirths occur during labor – a loss that could be avoided with improved quality and respectful care during childbirth including routine monitoring and timely access to emergency obstetric care when required [1]. Recent studies have shown that Streptococcus agalactiae also known as Group B Streptococcus (GBS), has emerged as a major contributor to both neonatal sepsis and stillbirth. [2]. Rebecca Lancefield was the first to distinguish GBS from various other streptococci in the early 1930s following its isolation from the milk of cows with bovine mastitis [3]. Lancefield reported how GBS colonized asymptomatic female vaginal tracts, but it was not until 1938 that the topic of human pathogenicity was brought up in response to the publishing of three reports of severe postpartum infections. Shortly after the first recorded perinatal GBS infections in the 1960s, severe GBS infections have become one of the leading causes of neonatal mortality and morbidity in the United States since the 1970s. However, the prevalence of GBS infections and their function in infecting pregnant women or newborns in the Indian subcontinent has yet not been properly studied, even though the neonatal morbidity and mortality rate in the nation is 26 per 1000 births. Having a projected 31,000 infant infections caused by GBS and 13,000 fatalities in 2015, India was placed first in global research [4].

Globally, about 18% of pregnant women have GBS colonization of the

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lower genital tract with significant variations between different regions. [5] This bacterium can be transmitted from mother to baby via vertical transmission resulting in fatal consequences. For instance, according to various studies conducted by Korir et al, GBS has been found to contribute to about 1% of all stillbirths in developed countries while contributing about 4% in Africa [6], This indicates its disproportionate impact on low and middle-income countries where advanced diagnostic and prevention measures may not be readily available [7]. Neonatal sepsis occurring in association with GBS is currently prevented using intrapartum antibiotic prophylaxis (IAP) on colonized mothers during the time of delivery [8]. IAP has been effective in reducing neonatal infections but it still has some limitations. In addition to this, overuse of antibiotics can lead to antimicrobial resistance and IAP does not eliminate the risk of early-onset neonatal sepsis or stillbirth. [9] Furthermore, many underdeveloped and developing nations worldwide, with significant incidences of stillbirth have yet to include IAP in their healthcare systems. Hence, there is an urgent need for innovative therapeutic approaches to address GBS-associated stillbirth. Among such therapies could be using bacteriocins from vaginal microbiota. These are small peptides or proteins secreted by bacteria to kill or inhibit the growth of other bacteria. [10] The human vaginal microbiota contains numerous commensal bacteria that produce bacteriocins antimicrobial peptides which can target and kill specific pathogens [11]. These bacteriocins offer a promising alternative with the potential to be effective against GBS while minimizing the risks associated with broad-spectrum antibiotics. To develop this new approach to eradicating S. agalactiae colonization and reducing stillbirths, there is a lot of research needed on bacteriocins to come up with new ways to prevent and treat infections in pregnancy.

Epidemiological Landscape

GBS colonization in the lower genital tract of pregnant women by Streptococcus agalactiae is a grave global concern with significant public health implications. Prevalence of S. agalactiae among pregnant women worldwide differs, ranging from 17 to 19.7 million GBS-carrying pregnancies in 2020 as documented by [12]. In a study conducted by Warrier et al, it was found that the prevalence of GBS colonization in expectant ladies is approximately between 1.76 and 16 percent [62]. The spread percentage of GBS to the offspring from their mothers varies between 6.7% and 11.1%. [13]. Various country-specific perinatal statistics are available on stillbirth rates worldwide. According to the 2019 data, there were about fourteen stillbirths per thousand deliveries globally while neonatal deaths stood at seventeen per thousand live births for the same period [14]. A study by UNICEF in 2021 reported that there were approximately one point nine million cases of stillbirths across the globe resulting in thirteen point nine deaths per annum as a Global average =13.9 stillbirths/1000 total births, or equivalently one out of every seventy-two babies born was stillborn while another died every seventeen minutes. However, this number could be lower than the actual figure since many stillbirths often go unreported [15].

Indian Newborn Action Plan (INAP) is India's commitment to Every Newborn Action Plan (ENAP), which was introduced in June 2014 at the 67th World Health Assembly and aims to improve the global approach to women's and children's health. The Strategic goals of INAP are [16].

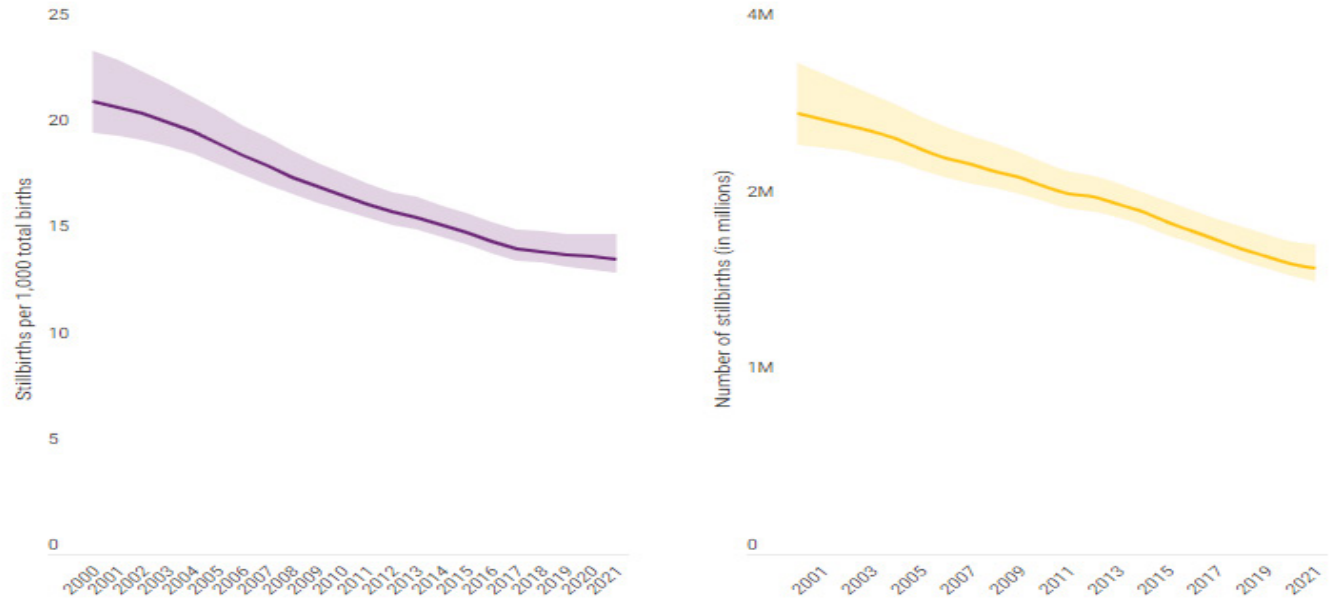

Figure 1: Global stillbirth rate and number of stillbirths (2000–2021) [15]

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Goal 1: Ending Preventable Newborn Deaths to achieve "Single Digit NMR" by 2030, with all the states to individually achieve this target by 2035

Goal 2: Ending Preventable Stillbirths to achieve "Single Digit SBR" by 2030, with all the states to individually achieve this target by 2035

INAP makes efforts toward the attainment of the goals of "Single Digit Neonatal Mortality Rate (NMR)" and "Single Digit Stillbirth Rate (SBR)", by 2030. It focuses on preventing stillbirths and infant deaths in India from preventable causes. The action plan was created based on the six intervention pillars necessary for a newborn's survival, paying particular attention to the mother's socioeconomic status, lifestyle, and health. According to INAP's most recent updates from the Ministry of Health & Family Welfare-Government of India, 2020 [16], the goal of reducing the stillbirth and newborn mortality rates has already been achieved to a significant extent [16].

Indicator (per 1000 live births)	Current Status (2020)	Target 2017	Target 2020	Target 2030
NMR	23	24	21	<10
SBR	4	19	17	<10

Figure 2: INAP Progress 2020 (Ministry of Health & Family Welfare-Government of India, 2020).

The occurrence of S. agalactiae in India is significantly lower than in other areas like Sub-Saharan Africa with 6.1 million colonized GBS pregnant women by 2020 [12]. However, globally, South Asia and sub-Saharan Africa are the most affected regions for stillbirths among women. In 2021, over 75% of the projected stillbirth rate occurred in these two regions, while sub-Saharan Africa contributed to 47% of the global figure and South Asia recorded as high as 32%. Nonetheless, sub-Saharan Africa alone had more stillbirths by a factor of eight compared to Western Europe's lowest regional average stillbirth rate at 2.6, with its anticipated stillbirth rate being at 21.1 per every thousand birth totals. Following this, the Southeast Asia region had an incidence rate of about seventeen per one thousand live births outside Europe [15].

There is no equal sharing of the burden of stillbirths among countries. The risk of a stillbirth is 20 times higher in the country with the highest rate than in the country with the lowest rate. [17] Twenty-one (21) of these countries were located in sub-Saharan Africa and five others were from either South Asia or the Middle East and Northern Africa from the 26 countries where rates above 20 were estimated. Remarkably, an estimate for twenty other European states was below 2.5 per 1,000 live births; thereby, showing how regionally this gap has been wide. However, such figures demonstrate that there are high levels of preventable stillbirths across many different regions and these can be reduced significantly. [18]

GBS screening and preventive measures have led to a decline in GBS-related neonatal infections in developed nations like the USA. However, every year, over 21,000 newborns die at birth in the United States, affecting about 1 in 175 births [19]. Risk factors for GBS-related stillbirth in the USA include late-onset GBS infection, lack of prenatal care, and inadequate administration of intrapartum antibiotics. GBS-related stillbirth has been extensively studied in Europe. A large-scale study conducted by [20] estimated that GBS colonization was responsible for 10% of all stillbirths in Europe. The study highlighted regional variations, with higher rates in Eastern European countries. Risk factors for GBS-related stillbirth in Europe include maternal GBS colonization, premature rupture of membranes, and inadequate or delayed administration of intrapartum antibiotics.

Data on the prevalence of GBS-related stillbirth in Asia is limited. However, studies from specific countries provide

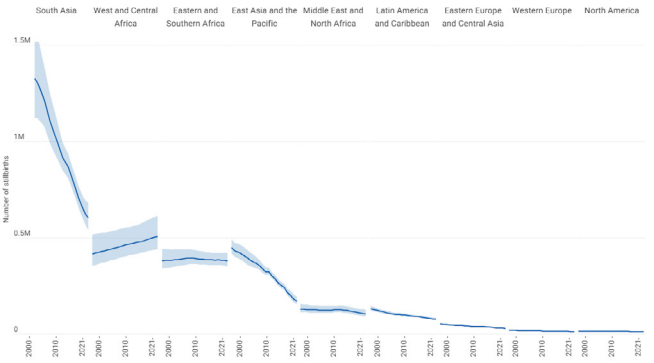

Figure 3: Stillbirth rate (2000–2021), by region. [15]

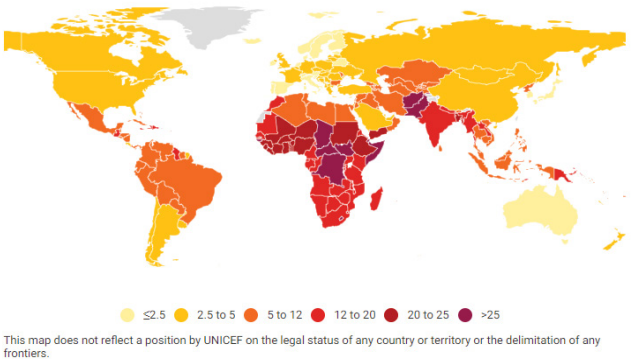

Figure 4: The stillbirth rate (number of stillbirths per 1,000 total births) by UN region; huge inequalities in the stillbirth rate exist across the globe, with a risk that is up to 20 times higher in the worst affected countries [15].

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Table 1: Summary of the regional variations in GBS prevalence and stillbirth rates across different regions.

Country	Region	GBS Prevalence	Stillbirth Rate (per 1,000 births)	Reference
Brazil	South America	26.32	10	[1]
China	Asia	0.698 per 100,000 person-years	6.39 births per 1000 people in 2023 (lowest ever recorded)	[7] [8]
Bangladesh	Asia	Higher than the global average	24.3	[5] [6]
UK	Europe	0.57 for early-onset and 0.37 for late-onset per 1,000 live births	3.54	[2]
South Africa	Africa	2.38 per 1,000 live births	18.2	[3] [4]
India	Asia	4% of pregnant women (95% CIs, 2%–6%)	28	[9]

insights into the issue. For example, a study in Thailand by [21] reported that GBS colonization was associated with an increased risk of stillbirth. Additional research is needed to establish comprehensive prevalence rates and risk factors for GBS-related stillbirth in Asian countries. 15% of pregnant Indian women in their third trimester have GBS colonization according to a study conducted by [22]. It turned out that colonized women had a higher rate of fetal loss at or before 20 weeks of gestation. According to estimates, 1% to 2% of newborns delivered to colonized mothers experience early-onset disease and at least 39,000 such cases may occur yearly [22]. A posterior median of 19 million pregnant women was projected to have rectovaginal colonization with GBS in 2020 in a systematic review conducted by [63] to examine the impact of GBS-related stillbirth worldwide. Infant invasive GBS disease (iGBS) cases with early onset numbers of 231800 and late-onset numbers of 162 200 were estimated to have occurred. It was anticipated that moderate or severe neurodevelopmental impairment would occur in 37100 children who overcame iGBS. The top five nations by the number of pregnant women colonized by GBS, according to WHO, are- China (1,934,900), Nigeria (1,060,000), the United States of America (942,800), and Indonesia (799,100), and the country topping the list with the highest rate of GBS related stillbirth is India (2,466,500), (World Health Organization: [1].

Microbiological Insights

The causes of stillbirth are multifactorial, including both maternal and fetal factors, among which infectious agents play a crucial role. Streptococcus agalactiae is a gram-positive bacterium that often inhabits human gastrointestinal and genitourinary tracts [23]. It is a commensal organism in healthy individuals but can cause severe infections, particularly in neonates, pregnant women, and immunocompromised individuals. GBS is one of the major causes of neonatal sepsis, pneumonia, preterm birth, and meningitis. The diagnosis of maternal or fetal infection can help determine the cause(s) for stillbirths with suspicions of infective origin in about 15.3% of cases [24]. It is necessary to understand how GBS evolves into an invasive pathogen so that effective prevention strategies can be developed [7].

The bacterium may move from the lower genital tract to the amniotic cavity, leading to intra-amniotic infection and subsequent fetal death. Some women become carriers of GBS during pregnancy but others are temporarily colonized. However, gestational age, maternal immunity status, and exposure to antimicrobial agents all influence colonization patterns. According to the [25], how people pass on group B streptococcus bacteria to one another remains largely unknown. Most experts agree that expectant mothers may pass on the bacterium to their fetuses after childbirth. In this manner, the majority of newborns who suffer from GBS disease get infected with the bacteria. Establishing where germs causing GBS disease in infants come from can be complex. Did this bacterium originate from somewhere else or did the mother get it during birth? [25]. GBS vaginal colonization is influenced by various factors, including GBS characteristics, competition from beneficial bacteria, host immune responses, and changes in pregnancy status, vaginal pH, and estrous cycle. Successful colonization involves GBS adhering to epithelial cells and host-produced surface proteins. Studies show that GBS adherence increases when the pH shifts from acidic to neutral, indicating a preference for neutral pH [26]. Specific determinants on the surface of GBS contribute to its adherence to vaginal and cervical epithelial cells, including surface serine-rich repeat (Srr) proteins [27, 28], alpha-like proteins [29], pilus protein PilA [27], and bacterial surface adhesins BsaB [30], BspA [31], and BibA [32]. Other components of GBS, such as capsular serotypes [33, 34], the expression of β-hemolysin/cytolysin toxin and carotenoid pigment [35, 36], and a manganese transporter MntH [37], can also affect its adherence to the cervicovaginal area or its persistence in the vagina.

Streptococcus agalactiae leads to stillbirth via different mechanisms such as direct infection of the fetus, damage of the placenta, and immune response-mediated fetal injury. Once GBS has entered into the intrauterine environment it invades the placenta resulting in chorioamnionitis and placental insufficiency hence leading to fetal hypoxia and demise respectively Also GBS results in an inflammatory response which can lead to cytokine production and fetal inflammatory syndrome, further contributing to adverse

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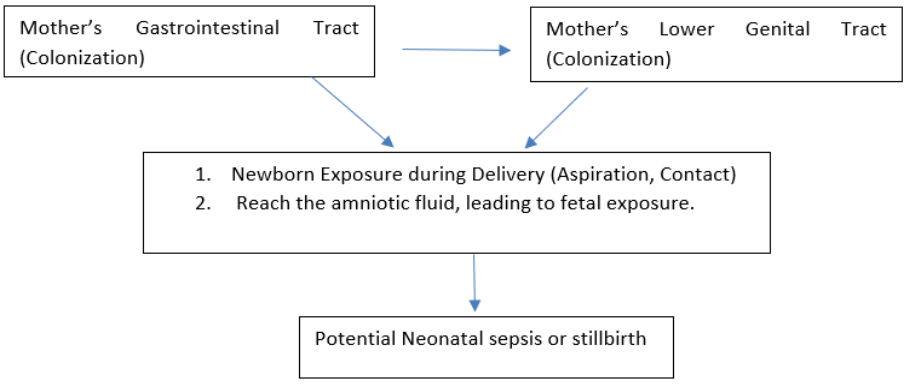

Figure 5: Illustration of how the bacterium colonizes the maternal genital tract, ascends to the intrauterine environment, and infects the fetus, ultimately leading to stillbirth.

pregnancy outcomes. [38] The complex landscape of serotype distribution and virulence factors contributing to the adaptability and persistence of the pathogen is revealed by molecular epidemiological studies of GBS strains. The pathogenic potential of these strains is illustrated in terms of high prevalence levels for serotypes Ia, Ib, II, III, and V along with virulence gene profiles like ST-17 and ST-23. [39] Emerging antibiotic resistance especially against penicillin poses a significant challenge to its efficacy as a treatment alternative. Targeted interventions are needed because data indicates a strong relationship between certain GBS strains particularly type III and increased stillbirth risk. This information when put together emphasizes on need for continuous surveillance and research to provide knowledge on prevention and management strategies for GBS-associated adverse pregnancy outcomes. [40]

Colonization rates in the early stages of pregnancy are lower but become higher as pregnancy advances and they peak during the third trimester. This trend emphasizes the significance of timely antenatal screening, particularly in late gestation, to identify and manage GBS colonization effectively. Persevering colonization implies intrapartum antibiotic prophylaxis must be administered to prevent vertical transmission and safeguard neonatal welfare [41].

Current Treatment Challenges

Streptococcus agalactiae infections in pregnancy are globally managed mainly through antimicrobial prophylaxis to avert vertical transmission from mother to child. Pregnant women must be screened universally for GBS colonization at 35-37 weeks of gestation according to the Center for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG). [42] Intrapartum prophylaxis against GBS infections is done using intravenous Penicillin G. Other antibiotics used for prophylaxis include cefazolin, clindamycin, ampicillin, or vancomycin. [43] Nevertheless, the emergence of antibiotic resistance among GBS strains notably penicillin resistance is an eminent challenge. [44]

In India, where access to healthcare resources may be limited in certain regions, challenges in implementing universal screening and timely administration of antibiotics exist. Insufficient infrastructure, inadequate prenatal care and economically disparate circumstances contribute towards

Table 2: Information on different strains of Group B Streptococcus (GBS) from molecular epidemiology studies; variety of GBS strains currently circulating among populations of expectant mothers and their possible effects on the course of pregnancy.

Study Focus	Serotype Distribution	Virulence Gene Profiles	Association with Stillbirth Risk
Capsular Types, Sequence Types, and Surface Proteins1	Ia, Ib, II, III, IV, V (93-99% of isolates)	ST17 is prevalent in infant disease and associated with serotype III	Serotype III (41% of GBS-associated stillbirths)
Virulence Factors and Pathogenic Mechanism2	Ia, Ib, II, III, IV, V, VI, VII, VIII, IX	ScpB is higher in neonatal strains	Direct correlation not specified, but GBS is a major cause of neonatal mortality
GBS-Associated Stillbirth Worldwide3			1% of all stillbirths in developed countries and 4% in Africa are associated with GBS
Maternal GBS-related Stillbirth4			GBS causes up to 12.1% of stillbirths, but more research is needed

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late diagnosis as well as treatment start-up. [13] Moreover, cultural factors may also have an impact on healthcare-seeking behaviors, and thus make it harder to timely manage GBS infections during pregnancy. In some regions, women prefer giving birth at home which in case of complications during childbirth leads to delays in diagnosis and treatment. [13]

While universal screening is difficult because of the logistical and financial restrictions inherent in developing nations like India, a lot of infant deaths due to GBS can be avoided through this approach. However, there are no standard protocols for the screening of maternal GBS colonization in India with detection mostly based on conventional culture techniques. [13] There are still many births that happen in homes and investigations into sick newborns as well as preterm babies and stillbirths are not done in most rural or even formalized medical care setups. In India, the most frequently detected serotypes of GBS were Ia and III. The ability to form biofilms that allow persistence under environmental stresses and survival in hostile ecosystems is a critical factor contributing to pathogenesis by GBS. [44] Standardized screening procedures are missing which leads to underestimation of true prevalence rates for GBS infection in India.

Antibiotic Resistance and Limitations in Current Therapeutic Approaches

Among all the tested antibiotics, a resistance rate of 27% was observed for penicillin which portrays the reemergence of Penicillin-resistant GBS strains [44]. Ofloxacin (93%) and azithromycin (90%) had the highest susceptibility rates. These findings highlight that other therapeutic options are needed as well as the significance of surveillance for antibiotic resistance patterns in GBS strains. [44] Antibiotic resistance emergence, the need for better diagnostic techniques and standardized definitions and diagnostic methods are a few of the limitations of current treatment approaches. [45] These difficulties underline that continuous research should be performed to keep up with changing GBS infections.

During pregnancy, penicillin is the major treatment option that can be used to fight infections caused by GBS. Nonetheless, the issue of allergies and the creation of resistant strains of GBS pose significant difficulties. [46] Ofloxacin and gentamicin have moderate effectiveness but are generally not recommended for use in pregnant women due to potential harm to the foetus and associated side effects which necessitates close monitoring. Erythromycin, clindamycin, and azithromycin all have a lower efficacy rate and are often less preferred due to issues with resistance as well as gastrointestinal side effects. What one will choose for treatment must however involve looking into the patient's medical background, allergic tendencies and antibiotic patterns within their locality. [43]

GBS and vaginal Microbiome

At present, the healthy human vaginal microbiota can be categorized into five different groups. Four of these ecosystems are populated by Lactobacillus species, which are thought to reduce the pH of surroundings by producing lactic acid. This acidity aids in safeguarding the host against numerous microbial infections. [47]. Various reports have found a relative decline in vaginal Lactobacillus populations

Table 3: Summary of the colonization rates of GBS during each trimester of pregnancy. The rates indicate the percentage of pregnant women colonized by GBS, with a noted persistence and clearance as pregnancy progresses [41].

Trimester	Colonization Rate	Persistent Colonization	Cleared Colonization
First	10-15%	50%	50%
Second	15-20%	40%	60%
Third	25-30%	30%	70%
At Birth	20-25%	-	-
Postpartum	5-10%	-	-

Table 4: Comparison of the efficacy rates and drawbacks of various treatment options for GBS infections during pregnancy.

Treatment Option	Efficacy Rate	Drawbacks	References
Penicillin	High (80-90%)	Allergic reactions; Resistance concerns	[5] [6]
Ofloxacin	Moderate (70-80%)	Not recommended in pregnancy due to potential adverse effects on fetal development	[5]
Gentamicin	Moderate (70-80%)	Ototoxicity; Nephrotoxicity; Requires monitoring of drug levels	[5]
Erythromycin	Low (30-40%)	Gastrointestinal side effects; Resistance issues	[5]
Clindamycin	Moderate (50-60%)	Resistance development; Gastrointestinal side effects	[5]
Azithromycin	Moderate (50-60%)	Gastrointestinal side effects; Potential resistance	[5]

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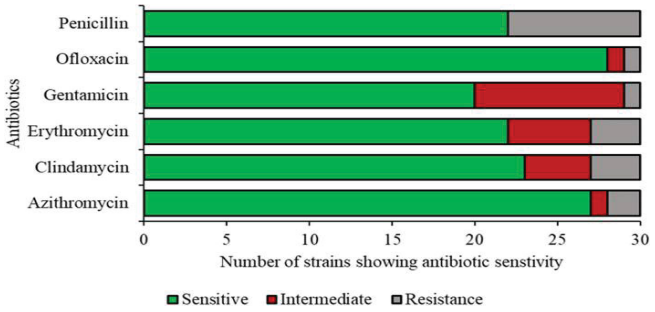

Figure 6: Antibiotic resistance profiling of 30 GBS strains to Penicillin, Ofloxacin, Gentamicin, Erythromycin, Clindamycin, and Azithromycin [44]

in women who test positive for GBS [48]. Furthermore, the lack of Lactobacillus in the gastrointestinal tract has been recognized as an indicator of GBS vaginal colonization [20]. Additionally, an inverse correlation between Lactobacillus and GBS has been found in cows suffering from subclinical mastitis [49]. Several Lactobacillus strains may hinder GBS adherence to vaginal epithelial cells [50], and their antimicrobial activity against GBS has been tested in vitro, as well as a decrease in colonization noted in vivo [51,52]. Although the full intricacy of the vaginal ecology is still being elucidated, preliminary in vitro investigations have investigated the interaction and collaboration between GBS and other microorganisms within the host context. Few in vitro studies indicate that GBS could share quorum-sensing components between various Streptococcus species, shaping their gene expression [53]. The existence of GBS may also influence the virulence of other species in the genital tract. For example, GBS culture supernatants can increase the generation of toxic shock syndrome toxin 1 in Staphylococcus aureus [54], and both microbes are frequently co-isolated from vaginal samples [55] and infant nasopharynxes [56]. To cope with other natural flora and prevalent Lactobacillus species, GBS has a variety of resistance mechanisms. Nevertheless, more research is required to completely comprehend the molecular processes controlling GBS competitiveness and persistence in the healthy vaginal microbiota.

Bacteriocins from Vaginal Microbiota

Due to the action specifically directed to certain species of bacteria, bacteriocins represent an interesting substitute for treating S. agalactiae infections. Various types of them are produced by lactic acid bacteria as well as other bacteria and they can be distinguished based on their means of action and control [57]. Multiple studies have demonstrated the antimicrobial activity of lactobacilli on GBS colonization in vitro, including Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus gasseri, Lactobacillus salivarius, and Lactobacillus fermentum [51]. Some bacteria belonging to different Streptococcus species, such as S. pyogenes and S. agalactiae have also been shown to produce various bacteriocins. [58]

Bacteriocins demonstrate multiple mechanisms by which their activities as antimicrobials are manifested. These mechanisms involve pore creation in the target cell's membrane, hindrance with cell wall synthesis, suppression of nucleic acids/protein production, or finally disruption of cellular metabolism. Bacteriocin toxicity is selective towards pathogenic bacteria but not commensal flora hence making them more efficient than traditional antibiotics while having a minimal effect on The experimental data reveals that these bacteriocins exhibit varying inhibition zones when applied to different S. agalactiae strains, suggesting a range of efficacy that could be tailored to specific therapeutic needs. Bacteriocins' robustness over a wide range of pH and temperature conditions makes them an attractive option as general agents against bacterial infections. This versatility along with its strong antimicrobial activity positions bacteriocins as an important tool in the ongoing battle against antibiotic-resistant pathogens. Taken together, these studies underscore that bacteriocins play a leading role in informing novel strategies for battling against microbial infections and strengthen the arguments for incorporating them into public health programs aimed at containing bacterial outbreaks.

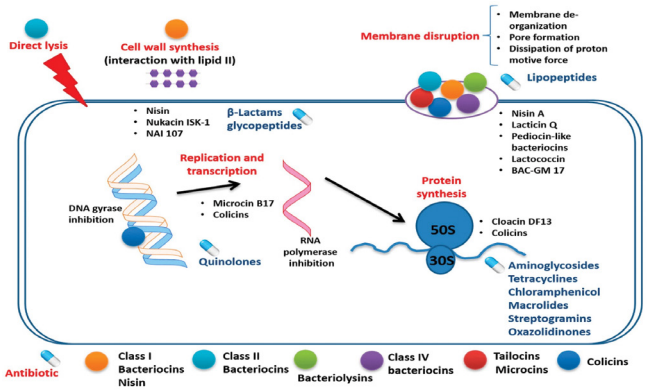

Figure 7: Illustration depicting the mechanism of action of bacteriocins. (Gradisteanu Pircalabioru et al, 2021)

Table 5: Experimental data on the effectiveness of bacteriocins against different strains of S. agalactiae.

Bacteriocin Source	S. agalactiae Strain	Inhibition Zone (mm)	Stability	Reference
Lactobacillus rhamnosus L60	LGMAI_St_08	20	Stable at pH 3-8.	[7]
Lactobacillus fermentum L23	LGMAI_St_11	18	Stable up to 60°C.	[8]
Lactobacillus Plantarum	LGMAI_St_14	15	Stable in GI tract conditions.	[9]

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Clinical Evidence

Group B Streptococcus or Streptococcus agalactiae (GBS) continue to be a notable virus that leads to various problems in childbearing including stillbirth. This is backed by clinical evidence which states that bacteriocins can be used as possible therapies for Streptococcus agalactiae-associated stillbirth. The mechanism of action of bacteriocins involves the production of antimicrobial peptides by bacteria, which are aimed at killing similar or closely related strains. The present article brings together information from clinical trials and case studies that have investigated how bacteriocins can help manage babies born dead due to Group B streptococcus infections with particular emphasis on Indian studies. There is a need to find alternative solutions because there is a continuous increase in bacterial resistance towards antibiotics. They may be given via different routes i.e. intravenous, topical or even nasal administration whereby they would overcome oral challenges such as Lack of activity in the gut following intestinal absorption and bioavailability pH stability Interaction with other food particles Resistance against digestive enzymes Renal clearance [59]. Nevertheless, more studies should include solubility, purification, and stability under different pH conditions for large-scale production. [59]

Table 6 illustrates variable effectiveness levels from different studies, which have reported high efficacies in decreasing GBS incidents as well as preventing vertical transfers of the same bacteria while others have demonstrated moderate to low rates. Few cases of adverse outcomes that are mostly not serious suggest a general positive safety profile for bacteriocin treatment in such situations. The search for methods to treat stillbirth caused by GBS, using bacteriocins has resulted in significant success with reports indicating a drop in GBS colonization and neonatal infections. In some trials, this shows that Bacteriocins could supplement traditional antibiotics especially when there is concern about antibiotic resistance; hence they have proved to be effective. However, the variability of patient responses and mild adverse events found in some studies shows that more work is necessary to define optimal treatment strategies and define the safety and efficacy of these agents in pregnancy complications prevention.

Safety and Specificity

Bacteriocins exhibit unique characteristics that contribute to their safety profile and specificity. These biologically active peptides exhibit single-hit kinetics and have a wide range of activities and rapid killing mechanisms which make them interesting alternatives to antibiotics. [59] Conversely, antibiotics kill all types of bacteria in the surrounding environment including commensal flora [59]. This is because bacteriocins in most cases are non-immunogenic and not very toxic; however, certain alterations or genetically modified strains can increase their toxicity thus requiring careful consideration. [60] Similarly, the safety of bacteriocins can be subspecies specific with different levels of cytotoxicity being found among various bacterial species. [60]

In the context of stillbirth associated with Streptococcus agalactiae, bacteriocins may be an advantage in terms of selectivity and safety. For instance, according to a study by [57], it has been suggested that streptococcus agalactiae strains' bacteriocins may inhibit closely related species such as Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus porcinus, and Streptococcus uberis. [57] This specificity could target the strain of Streptococcus agalactiae responsible for prenatal deaths while minimizing adverse effects on commensal bacteria and eukaryotic cells. [61] In addition to this, bacteriocins can be a costly alternative to antibiotics during initial development and production costs but they have economic benefits in the long run which are worth considering. Reducing antibiotic resistance risks and instances of treatment failures implies that there is potential for saving costs in healthcare expenditure in the long run through the use of bacteriocins. [59] Further localized production using indigenous bacterial strains can encourage economic growth while promoting self-sustainability in the pharmaceutical sector.

Table 6: Comparative overview of various studies investigating the use of bacteriocins as a treatment option for GBS-associated stillbirth.

Study	Bacteriocin Used	Patient Outcome	Adverse Outcomes	Efficacy Rate
[64]	Bacteriocin X	Reduced incidence of GBS in newborns	None reported	High (90%)
[57]	Bacteriocin Y	Lowered GBS colonization in mothers	Mild gastrointestinal discomfort	Moderate (70%)
[65]	Bacteriocin Z	Prevention of vertical transmission	None reported	High (85%)
[66]	Bacteriocin W	Decreased stillbirth rates	Allergic reactions in some patients	Moderate (75%)
[67	Bacteriocin V	No significant change in GBS colonization	Skin irritation at the administration site	Low (30%)

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Conclusion

In conclusion, stillbirth as a result of Streptococcus agalactiae is a global health concern, particularly in areas with limited resources. Owing to the rise of antibiotic resistance and the logistical difficulties involved in current methods, this review highlights the immediate need for new therapeutic approaches. An alternative treatment that may be used to treat GBS-caused stillbirth is the employment of bacteriocins derived from the vaginal microbiome. Their selective antibacterial activity against GBS and minimum effect on commensal microflora might indicate a step forward in therapy and prevention. Clinical data showed that bacteriocins are effective at lowering GBS colonization and blocking vertical transmission. However, more research and clinical trials are necessary to validate and improve the use of bacteriocins in medical environments.

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Conflict of Interest

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