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Interspecies Interactions within the Host: the Social Network of Group B *Streptococcus*

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ABSTRACT Group B *Streptococcus* (GBS) is a pervasive neonatal pathogen accounting for a combined half a million deaths and stillbirths annually. The most common source of fetal or neonatal GBS exposure is the maternal microbiota. GBS asymptomatically colonizes the gastrointestinal and vaginal mucosa of 1 in 5 individuals globally, although its precise role in these niches is not well understood. To prevent vertical transmission, broad-spectrum antibiotics are administered to GBS-positive mothers during labor in many countries. Although antibiotics have significantly reduced GBS early-onset neonatal disease, there are several unintended consequences, including an altered neonatal microbiota and increased risk for other microbial infections. Additionally, the incidence of late-onset GBS neonatal disease remains unaffected and has sparked an emerging hypothesis that GBS-microbe interactions in developing neonatal gut microbiota may be directly involved in this disease process. This review summarizes our current understanding of GBS interactions with other resident microbes at the mucosal surface from multiple angles, including clinical association studies, agriculture and aquaculture observations, and experimental animal model systems. We also include a comprehensive review of *in vitro* findings of GBS interactions with other bacterial and fungal microbes, both commensal and pathogenic, along with newly established animal models of GBS vaginal colonization and *in utero* or neonatal infection. Finally, we provide a perspective on emerging areas of research and current strategies to design microbe-targeting prebiotic or probiotic therapeutic intervention strategies to prevent GBS disease in vulnerable populations.

KEYWORDS vaginal microbiota, group B *Streptococcus*, probiotic, microbe-microbe interactions, *Streptococcus agalactiae*

Group B *Streptococcus* (GBS), or *Streptococcus agalactiae*, is a Gram-positive bacterium that is commonly found at the mucosa of the human gastrointestinal and vaginal tracts, along with the gastrointestinal tract of bovine species. Although typically an asymptomatic colonizer, GBS may disseminate to other tissues peripartum, such as the placental-fetal unit in pregnancy, the neonate during labor and delivery, or the mammary gland during lactation. In these environments, GBS can cause severe disease, including chorioamnionitis, preterm birth, stillbirth, neonatal sepsis or meningitis, or clinical mastitis (1–3). GBS is also an agent of skin and soft tissue infections, urinary tract infections, and sepsis; nonpregnant adults with underlying conditions such as diabetes or cardiovascular disease are at increased risk for such infections (4, 5). The global GBS colonization incidence in pregnancy is 18% (with regional variations from 11% to 35%) at any single point in time (6, 7). Colonization rates in nonpregnant adults are similar to those in pregnant individuals (8); however, cross-sectional studies may underestimate transient GBS colonization over time. In a 5-month longitudinal study of nonpregnant women, 79% of subjects were vaginally colonized with GBS in at least one of six visits (9). Similarly, in a pregnancy and postpartum study, the cumulative

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carriage rate of GBS was 54% (10). While GBS colonization may fluctuate within an individual and GBS strains may be eradicated or replaced with new GBS strains (11, 12), more typically, individuals are consistently colonized by the same strain or "clone" as determined by pulsed-field gel electrophoresis (10).

Current measures to prevent GBS neonatal disease consist of maternal recto-vaginal screening between 35 and 37 weeks of gestation, or risk factor screening, and administration of intrapartum antibiotic prophylaxis (IAP) to GBS$^+$ or at-risk individuals. This intervention has decreased GBS early-onset disease (EOD) from 1 in 500 live births (13) to 0.34 cases per 1,000 live births in the United States (14). The majority (~60%) of EOD cases occur in term infants born to women who were GBS$^-$ at the time of maternal screening, highlighting the need for further protocol optimization or implementation of additional testing upon hospital admission (14). Despite the exposure of ~30% of U.S. infants to IAP (14), universal screening and prophylactic treatment have not reduced late-onset disease (LOD) incidence. GBS LOD incidence has remained constant in North America and parts of Europe (15–18) and may even be on the rise in some regions (19, 20). GBS transfer between humans most often occurs through vertical transmission from mother to infant peripartum (21, 22) or through breastfeeding (23), although cocolonization between sexual partners or transmission through cohabitation has been reported (24, 25). GBS transmission in other species is less well characterized but can occur in dairy herds (26, 27) and in wild aquatic (28, 29) or aquaculture (30) settings. Since not all GBS-colonized individuals experience disease, it is imperative to understand how host-specific factors can protect against or aggravate complications arising from GBS carriage.

GBS AND THE HUMAN MICROBIOTA

Within its host, GBS does not exist in isolation. As a frequent member of the human gastrointestinal and vaginal microbiota, GBS has ample opportunity for microbial interactions. Although GBS can be a transient or permanent resident member of the human microbiota, it is not yet clear whether GBS is truly a commensal in this environment. Clinical and experimental studies examining GBS synergistic and antagonistic interactions with other microbes are summarized in Table 1 and Table 2 respectively.

Due to the importance of GBS vaginal colonization as a risk factor for neonatal disease, the majority of GBS-microbe interactions that have been identified so far are in the context of the vaginal tract. The human vaginal microbiome across demographics clusters into five distinct community state types (CSTs) based on sequencing of the 16S rRNA gene V3-V4 region (31). Four CSTs are dominated by a single *Lactobacillus* species, and one community (CST IV) is instead dominated by a mixture of anaerobic or facultative anaerobic organisms (31). In 16S rRNA sequencing-based nonpregnant vaginal studies, GBS colonization was observed across all five CSTs, but GBS abundance was highest in a non-*Lactobacillus* dominant CST, IV-A (32) (recently reclassified as CST IV-C1 [31]). Additionally, GBS$^+$ individuals displayed lower relative abundance of *Lactobacillus* than GBS$^-$ women (33) (Table 2). Inverse correlations between GBS and *Lactobacillus* species abundance have been corroborated in a microbial culture-based study (9). Several taxa correlate with GBS colonization status, although results differ between studies, potentially due to differences in cohort demographics or sequencing methodologies (e.g., taxonomy based on 16S rRNA V1-V2 versus V3-V4 sequences). In one study, GBS$^+$ individuals displayed higher levels of certain *Prevotella*, *Megasphaera*, and *Streptococcus* species than GBS$^-$ individuals (33) (Table 1). In another study, linear discriminant analyses identified positive associations with GBS and *Staphylococcus* spp., *Prevotella bivia*, and *Streptococcus* spp. and negative associations with GBS and bacterial vaginosis associated bacterium 1 (BVAB1), BVAB2, and other *Prevotella* and *Megasphaera* subgroups (32). In terms of pathogenesis, a culture-based study of nonpregnant women did not detect any differences in bacterial vaginosis (BV) incidence between GBS$^+$ and GBS$^-$ individuals (34). Furthermore, detection of vaginal pathogens, including *Candida albicans*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Chlamydia*

TABLE 1 Summary of synergistic interactions between GBS and other microbes from clinical and experimental studies[a]

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
Humans	*Bifidobacterim* spp.	Newborns of GBS^- and GBS^+ (and IAP-treated) mothers	Stool	52 newborns	Cross-sectional	IAP-exposed newborns have decreased gastrointestinal bifidobacteria, of which some strains were found to have antibacterial properties against GBS.	51
	Candida albicans	Nonpregnant	Urine and urogenital discharge	>2,400 participants	Cross-sectional	Urogenital GBS was coisolated with enterococci, *Staphylococcus saprophyticus*, and *C. albicans*.	193
		Nonpregnant	Not specified	56 participants	Retrospective	GBS was most common bacterial coisolate in a cohort of recurrent vulvovaginal candidiasis patient samples.	194
		Pregnant	Vaginal wash	13,914 participants	Prospective	*Candida* colonization was accompanied by GBS in 36.8% of samples collected.	195
		Pregnant	Vaginal swab	150 participants	Cross-sectional	*Candida* spp. were found in 14.9% of GBS^+ women compared to 2.9% of GBS^- women.	41
		Pregnant	Vaginal swab	623 participants	Cross-sectional	Of the 7% of healthy vaginal samples in which GBS was detected, *C. albicans* was coisolated in 54.5% of those samples.	42
	Candida spp.	Pregnant	Vaginal swab	7,742 participants	Cross-sectional	Risk of cervicovaginal colonization with GBS was increased with dual GBS and *Candida* sp. colonization.	196
		Pregnant	Vaginal swab	405 participants	Prospective	Risk of GBS colonization was increased in women cocolonized with *Candida*.	43
		Pregnant	Rectal and vaginal swab	100 participants	Cross-sectional	GBS prevalence was increased in women cocolonized with *Candida*.	197
		Pregnant	Vaginal swab	221 participants	Longitudinal	GBS and *Candida* were coisolated in 26.6% of samples.	198
	Candida spp. *Enterococcus* spp. *Staphylococcus aureus*	Pregnant	Vaginal swab	542 participants	Cross-sectional	GBS and *Candida* were coisolated in 36% of GBS^+ samples.	132

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TABLE 1 (Continued)

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
	Candida albicans *Escherichia coli*	Pregnant and nonpregnant	Vaginal swab	430 participants	Cross-sectional	GBS had a higher risk of detection in samples with *C. albicans* (37.0%) and *E. coli* (24.6%) than in those without dual colonization. Conversely, *E. coli* had a higher risk of detection in GBS^+ (43.3%) vs GBS^- samples.	44
	Escherichia coli	Nonpregnant	Midstream and catheter urine	202 paired samples	Cross-sectional	GBS and *E. coli* were cocultured from midstream urine and catheter urine collections.	167
		Pregnant	Urine	821 participants	Retrospective	GBS and *E. coli* were cocultured from uterine cultures taken during nonelective cesarean sections.	163
		Nonpregnant	Endocervical swab	61 participants	Randomized trial	Of participants using a candidate HIV prophylactic, the GBS concn was inversely associated with inhibitory activity against *E. coli*.	165
	Escherichia coli Yeast	Nonpregnant	Rectal and vaginal swab	1,248 participants	Prospective	Rectal GBS colonization is a predictor of GBS vaginal colonization. Other risk factors for GBS vaginal colonization include concurrent vaginal *E. coli* or yeast colonization.	162
	Escherichia coli *Staphylococcus aureus*	Women diagnosed with vulvovaginitis	Vaginal swab	4 participants	Case study	GBS was coisolated with *E. coli* and *S. aureus*.	148
	Escherichia coli *Eubacterium lentum* *Porphyromonas* spp. *Prevotella* spp. *Salmonella* sp. *Staphylococcus* spp. *Streptococcus viridans*	Women diagnosed with tubo-ovarian abscess	Laparotomy drainage	11 participants	Case study	GBS was coisolated with multiple aerobic and anaerobic microbes.	164
	Atopobium vaginae *Bifidobacterium* spp. *Megasphaera* sp. *Prevotella* spp.	Pregnant	Vaginal swab	248 participants	Prospective	GBS^+ samples correlated with different species depending on thresholds set and analysis via cultivation or WGS.	46

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TABLE 1 (Continued)

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
	Clostridiaceae *Enterococcaceae* *Ruminococcaceae*	Infants of GBS$^+$ mothers	Stool	298 participants	Longitudinal	Once adjusted for demographic parameters and use of IAP, GBS$^+$ status in mothers was associated with variation in gut microbiota composition in samples from the 6-mo visit.	50
	Bacteroidetes *Bacteroidia* *Bacteroidales* *Clostridia* *Clostridiales* *Megasphaera* *Prevotella* *Prevotellaceae* *Veillonellaceac*	Nonpregnant	Vaginal swab	66 participants	Cross-sectional	After filtering for taxa with a logarithmic discriminant analysis score of ≥3, 10 taxa were positively associated with GBS$^+$ status. Note that *Streptococcus* as a correlate has been omitted since it was not distinguished from GBS.	33
	Prevotella spp.	Diabetic patient	Scrotal abscess	1 participant	Case study	GBS and *Prevotella* were cocultured.	187
		Pregnant	Vaginal swab	72 participants	Prospective longitudinal	Of the women who received IAP for GBS, *Prevotella* relative abundance increases postpartum.	185
	Eubacterium siraeum *Finegoldia magna* *Prevotella bivia* *Prevotella melaninogenica* *Peptostreptococcus anaerobiius* *Staphylococcus* spp. *Veillonella* spp.	Nonpregnant	Vaginal lavage specimen	432 participants	Cross-sectional	After filtering for taxa with a logarithmic discriminant analysis score of ≥2.5, 8 taxa were positively associated with GBS$^+$ status.	32
	Staphylococcus aureus	Pregnant	Vaginal swab	4,025 participants	Cross-sectional	GBS$^+$ status was associated with reduced coculture with Gram-positive cocci, anaerobes, and fungi, but also an increased association with specific microbes.	40

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TABLE 1 (Continued)

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
	Klebsiella pneumoniae						
	Staphylococcus aureus	Nonpregnant	Sterile site culture	19,512 samples	Population-based surveillance	*S. aureus* was the most common coisolate (46.2%) in GBS polymicrobial sepsis cases.	139
		Nonpregnant	Blood	94 cases	Retrospective	GBS was most commonly coisolated with *S. aureus* or *K. pneumonia*.	142
		Patients diagnosed with pneumonia	Blood and respiratory samples	1,791 cases	Retrospective	Of those identified with polymicrobial cultures, 20% were coisolated with *S. aureus* and 7% with *P. aeruginosa*	143
		Patients diagnosed with bone or joint infection	Deep surgical sample, joint aspirate, or blood	26 cases	Retrospective	GBS was found more often in polymicrobial than monomicrobial infections. *Staphylococcus* spp. (*S. aureus* and *S. ludgunesis*) and *E. faecalis* were found in 56% and 19% of samples, respectively.	144
		Men	Skin, urinary or respiratory tract, blood, abscess, joint, bone, or unknown	23 cases	Retrospective	Of patients with bacteremia, GBS was coisolated with *B. fragilis*, other beta-hemolytic *Streptococcus* spp., *S. aureus*, and *Providencia stuartii*.	140
		Nonpregnant adults and neonates	Blood	18 cases	Retrospective	*S. aureus* was the most common coisolate in GBS bacteremia.	141
		Infants	Nasopharyngeal swab	1,200 participants	Cross-sectional	Risk of GBS colonization increased with the detection of *S. aureus*.	137
		Pregnant	Rectal and vaginal swab	2,963 samples	Prospective	*S. aureus* prevalence was increased in GBS^+ samples.	127
		Pregnant women and neonates	Rectal and vaginal swab	2,702 women and 2,789 infants	Retrospective	Risk of *S. aureus* colonization increased with the detection of GBS.	131
		Pregnant	Rectal and vaginal swab	2,921 samples	Prospective	GBS colonization was positively associated with *S. aureus*.	130
		Pregnant	Vaginal swab	6,626 participants	Cross-sectional	Risk of *S. aureus* colonization increased in patients with GBS.	128
		Pregnant	Rectal and vaginal swab	5,732 participants	Prospective	Risk of *S. aureus* colonization increases with positive GBS colonization status.	129
	Trichomonas vaginalis	Patients with vaginitis	Vaginal swab	327 participants	Cross-sectional	GBS was positively associated with *T. vaginalis* infection.	35
Cows (Holstein)	*Aeromonas* spp.	Dairy herds	Milk	7 cows	Cross-sectional	GBS^- subclinical mastitis milk was dominant in *Firmicutes* and was associated with an increase in 2 taxa.	3

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TABLE 1 (Continued)

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
	Chryseobacterium spp.						
Mice (KK-A^{y})	*Klebsiella pneumoniae*	Laboratory colony	Submandibular abscess and uterine tissue	2 mice	Case study	Of the cultures taken from submandibular abscesses, *K. pneumoniae* was coisolated. Of the 1 uterine culture, *S. aureus* was coisolated.	119
	Staphylococcus aureus						
Rats	*Staphylococcus* spp.	Pups from MWF-hDTR laboratory colony	Spleen, kidney, and heart	4 rats	Case study	GBS was cocultured with coagulase-negative *Staphylococcus* spp. in limb abscesses, and *E. coli* was coisolated from a liver.	120
	Escherichia col						
	Escherichia coli	Female adults from Long-Evans laboratory colony	Spleen, vaginal swab, cervical, nares, lung, brain, uterine, fetal, cardiac thrombus	2 rats	Case study	GBS was coisolated with multiple microbes from different tissue sites or lavage specimens.	121
	Enterobacter aerogenes						
	Enterococcus spp.						
	Staphylococcus sciuri						
	Streptococcus mitis						
	Streptococcus oralis						
Exptl models	**Interaction**	**Condition/intervention**	**Sample type or medium**	**Sample size**		**Key finding(s)**	**Reference**
In vivo							
Mice (CD-1)	*Akkermansia municiphila*	GBS challenge following pretreatment or cocolonization with *A. muciniphila*	Vaginal lavage specimen	Not specified		GBS persistence in the vaginal lumen was increased in mice dually colonized with *A. muciniphila*.	175
Nile tilapia	*Akkermansia* spp.	Oral gavage with GBS strain YM001	Intestinal tissue	30 fish		Administration of YM001 caused temporary and nonlethal changes in the intestinal gut microbiota, making it a safe vaccine.	106
	Bacteroides spp.						
Mice							
C57BL/6J	*Candida albicans*	Transurethral coinfection of *C. albicans* and GBS	Bladder	14–18 mice/group		*C. albicans* increased GBS colonization and epithelial adherence through hypha-specific adhesin Als3.	200
		Vaginal coinoculation of *C. albicans* and GBS	Vaginal lavage specimen	6 mice/group		The vaginal mucosal Th17 response to *C. albicans* is reduced in the presence of GBS.	199

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TABLE 1 (Continued)

Exptl models	Interaction	Condition/intervention	Sample type or medium	Sample size	Key finding(s)	Reference
C3H/HeN and C3H/HeJ	*Escherichia coli*	Urinary tract coexposure to GBS and UPEC	Bladder	>10 mice/group	Immune response against UPEC is dampened by GBS sialic acid host immune signaling.	168
C57BL/6J	*Gardnerella vaginalis*	Vaginal coinoculation of GBS and *G. vaginalis*	Maternal vaginal, uterine, and placental tissues	31 mice	Risk for vaginal colonization, ascension into the uterus, and presence in both the maternal and fetal sides of the placenta increase in the presence of *G. vaginalis*.	192
Rats (Wistar)	*Prevotella bivia*	Uterine inoculation with *P. bivia* and GBS	Uterine fluid	10 rats/group	*P. bivia* uterine infection is increased by GBS.	186
In vitro	*Candida albicans*	*C. albicans* and GBS coculture *in vitro*	Spider agar and YPD	Triplicate	GBS suppresses hyphal formation through reduction of EFG1/Hwp1 expression.	199
		Cocultivation of *C. albicans* and GBS	Yeast nitrogen base	Triplicate	GBS BspA protein promoted association of GBS with *C. albicans* hyphae.	201
		Cocultivation of *C. albicans* and GBS and cocolonization of vaginal epithelial cells	Keratinocyte serum-free medium	Triplicate	Interaction between GBS and *C. albicans* increases with hyphal form via *C. albicans* adhesin Als3 and GBS Bsp adhesins.	202
		Cocultivation of *C. albicans* and GBS	Blood agar	110 *C. albicans* strains	*C. albicans* and GBS demonstrate cohemolytic (CAMP factor like) activity.	203
	Escherichia coli	Cross-feeding assays on solid media and liquid culture	M17 glucose agar	Not specified	*E. coli* produces ubiquinone, menaquinones, and other metabolites that may be utilized by GBS.	166
	Staphylococcus aureus	Culture of *S. aureus* with supernatants from bacteria associated with dysbiosis and health	BHI	Not specified	GBS supernatant increased *S. aureus tst* gene expression encoding toxic shock syndrome protein TSST-1.	145
		Coculture of GBS with bacterial species commonly found in female genital tract	TSB agar	Not specified	*S. aureus* was not inhibited by GBS isolates.	146

[a]sp., single unspecified or unknown species of a genus; spp., more than one unspecified or unknown species of a genus; IAP, intrapartum antibiotic prophylaxis; UPEC, uropathogenic *E. coli*; YPD, yeast extract-peptone-dextrose; BHI, brain heart infusion; TSB, tryptic (or Trypticase) soy broth.

TABLE 2 Summary of antagonistic interactions between GBS and other microbes from clinical and experimental studies[a]

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
Humans	BVAB1	Nonpregnant	Vaginal lavage	428 samples	Cross-sectional	The abundances of 6 taxa were negatively associated with GBS$^+$ status. Communities clustered according to GBS status on principal-component analysis, but the contribution of GBS status to overall variance was small. GBS presence was associated with community state type IV subgroup analysis, where 40% of subgroup A samples were GBS$^+$ compared to 17% in subgroup IV-B.	32
	BVAB2 *Dialister* sp. type 2 *Megasphaera* sp. type 1 *Prevotella* genogroup 3 *Prevotella* genogroup 4						
	Candida spp. *Enterococcus faecalis* *Lactobacillus* spp. *Peptostreptococcus* spp. *Prevotella* spp. *Staphylococcus* spp. (coagulase negative) *Streptococcus* spp. (microaerophilic)	Pregnant	Vaginal swab	4,025 participants	Cross-sectional	From a collection of strains isolated from vaginal samples; 8 taxa were associated with the GBS-negative group.	40
	Lactobacillus helveticus *Lactobacillus mudanjiangensis* *Lactobacillus paracasei* *Staphylococcus lugdunensis*	Infants of GBS$^+$ mothers	Stool	86 samples	Cross-sectional	α diversity did not differ based on GBS status. Communities clustered similarly on principal-component analysis regardless of GBS status. The abundances of 4 taxa were negatively associated with GBS$^+$ status.	49

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TABLE 2 (Continued)

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
	Bacilli (class)	Nonpregnant	Vaginal swab	66 participants	Cross-sectional	α diversity did not differ based on GBS status. Communities clustered according to GBS status on principal-component analysis, but the contribution of GBS status to overall variance was small. LEfSe analysis revealed 5 taxa negatively associated with GBS$^+$ status.	33
	Firmicutes (phylum) *Lactobacillaceae* (family) *Lactobacillales* (order)						
	Lactobacillus spp.	Nonpregnant	Vaginal swab	191 participants	Longitudinal with intervention	In vaginal samples classified by amt of lactobacilli, GBS prevalence was lower in samples with avg or large amt of high lactobacilli vs samples with small amt of lactobacilli.	9
		Nonpregnant receiving IVF	Vaginal swab	285 participants	Prospective	Small amounts of Lactobacilli, classified as $<10^4$ CFU, were associated with GBS positive status.	211
	Lactobacillus spp.	Pregnant	Vaginal swab	1,860 samples	Retrospective cross-sectional	Presence of lactobacilli, specifically *L. crispatus*, was negatively correlated with GBS$^+$ status.	191
	Lactobacillus crispatus						
	Lactobacillus reuteri and *Lactobacillus rhamnosus*	Pregnant	Vaginal and rectal swab	110 participants	Prospective with intervention	42.9% of GBS$^+$ participants treated with a combination of *L. rhamnosus* and *L. reuteri* early in pregnancy became GBS$^-$ by the time of delivery, while 18% became GBS$^-$ in placebo group.	278
		Pregnant	Vaginal secretions	155 participants	Longitudinal with intervention	The group receiving oral *Lactobacillus* probiotic treatment had significantly reduced incidence of premature rupture of membranes but did not significant impact GBS clearance.	279

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TABLE 2 (Continued)

Host or model	Interaction	Population or condition/ intervention	Sample type or medium	Cohort or sample size	Study type	Key finding(s)	Reference
	Lactobacillus salivarius	Nonpregnant and pregnant	Vaginal and rectal swab	54 participants	Longitudinal with intervention	Of GBS$^+$ participants treated with *L. salivarius*, 78% became rectally GBS$^-$ and 68% became vaginally GBS$^-$, while none became rectally or vaginally GBS$^-$ in the control group.	284
	Lactobacillus sp.	Pregnant	Vaginal swab	150 participants	Cross-sectional	From a collection of strains isolated from vaginal samples, *Lactobacillus* species were associated with the GBS$^-$ status.	41
	Lactobacillus crispatus *Neisseria* spp.	Pregnant	Vaginal swab	243 samples	Longitudinal	The relative abundances of 2 taxa negatively co-occurred with GBS presence.	46
	Aerococcus spp.	Pregnant	Vaginal swab	94 participants	Cross-sectional	*Aerococcus* relative abundance was lower in the GBS$^+$ group.	45
Cows (Holstein)	*Acinetobacter* spp. *Corynebacterium* spp. *Microbacterium* spp. *Stenotrophomonas* spp.	Dairy herds	Milk	12 cows	Cross-sectional	The relative abundances of 4 genera were lower in the GBS$^+$ group.	103
	Lactobacillus spp.	Dairy herds	Milk	40 cows	Cross-sectional	As determined by qPCR, *Lactobacillus* quantity was negatively correlated with GBS quantity.	212

Exptl models	Interaction	Condition/intervention	Sample type or medium	Sample size	Key finding(s)	Reference
In vivo						
Mice						
BALB/c	*Lactobacillus reuteri*	Vaginal *L. reuteri* administration	Vaginal washes	14 mice	*L. reuteri* inhibited GBS vaginal colonization.	213
C57BL/6J	*Staphylococcus* spp.	Vaginal inoculation with GBS	Vaginal swab	72 mice	Upon GBS colonization, *Staphylococcus*-dominant vaginal microbiota were less stable.	122
	Staphylococcus succinus	Vaginal inoculation with GBS	Vaginal swab	32 mice	*S. succinus* relative abundance decreased over time in GBS infection.	123
CD-1	*Streptococcus salivarius*	Vaginal inoculation with GBS and treatment with *S. salivarius*	Vaginal swab	Not specified	*S. salivarius* reduced GBS vaginal colonization.	206
Nile tilapia	*Brevinema* spp.	Oral inoculation with attenuated GBS strain	Intestinal tissues	105 fish	Attenuated GBS temporarily impacted gut microbiome by reducing diversity and changing composition.	106

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TABLE 2 (Continued)

Exptl models	Interaction	Condition/intervention	Sample type or medium	Sample size	Key finding(s)	Reference
	Cetobacterium spp. *Romboutsia* spp.					
	Enterococcus faecium	Treatment with *E. faecium* and i.p. injection with GBS	Stool	45 fish	*E. faecium* treatment reduced mortality in GBS-infected fish.	297
	Lactobacillus rhamnosus and *Lactococcus lactis* subsp. *lactis*	Treatment with *L. rhamnosus* and *L. lactis* and i.p. injection with GBS	Intestinal tissues	720 fish	*L. rhamnosus* and *L. lactis* treatment increased GBS disease resistance.	298
	Clostridium butyricum	Treatment with *C. butyricum* and i.p. injection with GBS		225 fish	*C. butyricum* treatment reduced mortality in GBS-infected fish.	299
	Bacillus cereus and *Bacillus subtilus*	Treatment with *B. cereus* and/or *B. subtilis* and i.p. injection with GBS		100 fish	Combined probiotic and *B. cereus*-only treatments reduced mortality in GBS-infected fish.	300
In vitro						
	Diphtheroids *Enterococcus* spp. *Gardnerella vaginalis* Group A *Streptococcus* Group B *Streptococcus* (other than test strain) Group C or G *Streptococcus* *Lactobacillus* spp. *Peptostreptococcus* spp. *Streptococcus* spp. (alpha-hemolytic) *Streptococcus* spp. (nonhemolytic)	Agar overlay inhibition assay	Strains grown in TSB with 5% sheep blood, assay on TSB agar	Duplicate	GBS inhibited the growth of many, but not all, tested bacterial strains found in the vaginal tract.	146
	Bacillus altitudinis *Bacillus amyloliquefaciens* *Bacillus pumilus* *Streptomyces rutgersensis*	Agar overlay inhibition assay	Isolates derived from intestinal tissues; assay on LB agar	Triplicate	Some fish gut bacterial isolates inhibited GBS growth.	301
	Bifidobacterium breve *Bifidobacterium longum* subsp. *longum*	Agar overlay inhibition assay	*Bifidobacterium* in TPY; GBS in BHI	Triplicate	Some bifidobacterial strains inhibited GBS growth.	51
	Streptococcus salivarius	Coculture and deferred antagonism	THB and Columbia blood agar	Triplicate	*S. salivarius* inhibits the growth of GBS in coculture and through secreted substrates.	206

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TABLE 2 (Continued)

Exptl models	Interaction	Condition/intervention	Sample type or medium	Sample size	Key finding(s)	Reference
		Transwell coculture; cell-free supernatant treatment	THB	Triplicate	GBS inhibited growth of *S. salivarius* via coculture and supernatant, but inhibition was reversed by galacto-oligosaccharide treatment.	207
	Lactobacillus acidophilus	Bacteriocin treatment of GBS culture	BHI	Not specified	*L. acidophilus* bacteriocin inhibited GBS growth.	222
	Lactobacillus fermentum	Agar well diffusion assay	TSB agar	Not specified	*L. fermentum* bacteriocin inhibited GBS growth.	218
	Lactobacillus crispatus *Lactobacillus gasseri* *Lactobacillus reuteri*	Cell-free supernatant treatment	TSB	Triplicate	*L. reuteri* and *L. gasseri* supernatants inhibited GBS growth; all 3 species supernatants inhibited GBS biofilm formation and association with human endometrial stromal cells.	214
	Lactobacillus acidophilus *Lactobacillus paracasei*	GBS adhesion assay with *Lactobacillus* inhibition by exclusion, competition, or displacement	LAPTg	Triplicate	*Lactobacillus* strains inhibited GBS adhesion to human vaginal epithelial cells.	215
	Lactobacillus crispatus *Lactobacillus gasseri*	GBS adhesion assay with *Lactobacillus* inhibition by exclusion, competition, or displacement	Not specified	Triplicate	All *L. crispatus* and *L. gasseri* strains inhibited GBS adhesion to human vaginal epithelial cells by exclusion, competition, and displacement.	216
	Lactobacillus crispatus *Lactobacillus gasseri* *Lactobacillus vaginalis*	Coculture and cell-free supernatant treatment	Horse blood agar and MRS with L-cysteine	Duplicate	Multiple *Lactobacillus* strains and supernatants inhibited GBS growth.	220
	Lactobacillus fermentum *Lactobacillus rhamnosus*	Streak-diffusion agar inhibition assay	MRS and TSB	Duplicate	*Lactobacillus* bacteriocins inhibited GBS growth.	223
	Lactobacillus fermentum *Lactobacillus rhamnosus*	Agar well diffusion assay	MRS and TSB	Triplicate	Bacteriocins from either *Lactobacillus* strain and a combination of their bacteriocins inhibited growth of most GBS strains.	224
	Lactobacillus paracasei subsp. *paracasei*	Microdilution antimicrobial assay	MRS and TSB	Triplicate	*Lactobacillus* biosurfactant inhibited GBS growth.	225

(Continued on next page)

TABLE 2 (Continued)

Exptl models	Interaction	Condition/intervention	Sample type or medium	Sample size	Key finding(s)	Reference
	Lactobacillus gasseri	Agar well diffusion assay	LAPTg	Not specified	*Lactobacillus* supernatants inhibited GBS growth.	227
	Lactobacillus salivarius					
	Lactobacillus salivarius (multiple strains)	Agar overlay, agar well diffusion, coaggregation, and coculture assays	MRS	Triplicate for agar diffusion. Not specified for other assays.	GBS growth was inhibited in agar overlay with *L. salivarius*, but not in agar well diffusion using *L. salivarius* supernatants. Some *L. salivarius* strains coaggregated with some GBS strains. Compared to GBS monoculture, most *L. salivarius* strains interfered with GBS growth in co-culture.	284

[a]BVAB1 and BVAB2, bacterial vaginosis-associated bacterium 1 and 2; sp., single unspecified or unknown species of a genus; spp., more than one unspecified or unknown species of a genus; IVF, *in vitro* fertilization; i.p., intraperitoneal; subsp., subspecies; TSB, tryptic (or Trypticase) soy broth; LB, Luria-Bertani (or lysogeny broth); TPY, tryptone-peptone-yeast; BHI, brain heart infusion; THB, Todd Hewitt broth; LAPTg, cultivation medium composed of 1.5% peptone, 1% tryptone, 1% glucose, 1% yeast extract, and 0.1% Tween 80; MRS, de Man Rogosa Sharpe.

trachomatis, was not influenced by GBS colonization status (34); however, in another study, GBS colonization was enriched in individuals with *T. vaginalis* infection (35).

Pregnancy studies also report mixed clinical findings, which may be driven by biological differences across cohorts, including subject demographics and gestational length at the time of sampling, which are both known to impact the vaginal microbiota composition (36–38). Methodological differences ranging from targeted cultivation or quantitative PCR (qPCR) to broader sequencing approaches, including 16S rRNA amplicon profiling or whole-genome sequencing, may also influence study outcomes. As with nonpregnant women, GBS colonization itself does not indicate an altered or aberrant vaginal microbiota or clinical disease, such as BV, but distinct correlations with individual taxa and GBS have been reported. One culture-based study of 3,596 pregnant women found that patients diagnosed with BV had lower GBS colonization rates than non-BV controls (39). In another culture-based study of 4,025 pregnant women, midgestation GBS colonization was associated with lower levels of *Lactobacillus*, *Prevotella*, and *Candida* and higher levels of *Staphylococcus* (40) (Table 1 and Table 2). A smaller (150 subjects) midgestation culture-based study also observed reduced *Lactobacillus* in GBS^+ subjects, but in contrast, reported GBS coisolation with *C. albicans* (41). In culture-based studies of late-gestation samples, GBS was coisolated with *C. albicans* (42) or individuals with candidosis (43). In a longitudinal pregnancy study of 42 women sampled at each trimester, no significant differences in levels of *Lactobacillus*, *Bifidobacterium*, or *Candida* were observed between GBS^+ and GBS^- individuals as measured by cultivation and qPCR of target species (11). In another qPCR-based study consisting of both pregnant and nonpregnant subjects, GBS was coisolated with *C. albicans* and *Escherichia coli*, and GBS^+ individuals had a reduced incidence of BV (44). In a 16S rRNA amplicon study of 94 women during late gestation, the GBS^+ group displayed decreased *Aerococcus* and increased *Corynebacterium* abundance, as well as an increased but nonsignificant abundance of *Lactobacillus* spp. (45). Finally, in a whole-genome sequencing study conducted in 248 pregnant women, GBS colonization was negatively associated with *Lactobacillus crispatus* and positively associated with 19 species, including multiple *Prevotella* spp., *Bifidobacterium* spp., *Atopobium vaginae*, and other *Streptococcus* spp. (46). The vast majority of vaginal studies to date have binned subjects into GBS^+ and GBS^- groups based on culture results, and thus potential ecologic relationships between GBS abundance and other organisms remain undiscovered. Future studies designed to broadly capture GBS-microbe associations, such as whole-genome sequencing, might establish microbial relationships that hold predictive value for host outcomes or inform therapeutic interventions.

Outside of the context of the vaginal microbiota, there are fewer data reporting GBS associations with the host microbiota. If GBS influences the presence or absence of other organisms, either directly through niche competition or indirectly through host immune or metabolism modulation, it is feasible that GBS presence in the maternal vagina may alter maternal microbial transfer to the infant or the establishment of the infant microbiota. Maternal microbial transfer may be further perturbed by IAP; studies have reported reduced vaginal *Lactobacillus* spp. in the IAP group compared to women without IAP (47, 48). In general, no large differences in fecal α or β diversity are observed in infants born to GBS^+ mothers (49, 50). One study found reduced *Staphylococcus lugdunensis* and *Lactobacillus* spp. in infants born to GBS^+ mothers; however, IAP effects were not accounted for in this cohort since no significant differences in the rates of IAP between GBS^+ and GBS^- groups were observed (49). Clinical observations report differences in abundance for taxa including *Ruminococcus*, *Clostridium*, *Akkermansia*, and *Bacteriodes* in infant fecal samples between infants born to GBS^+ mothers and those born to GBS^- mothers even when adjusting for other factors such as IAP (50) (Table 1). *Bifidobacterium* abundance is reduced in the fecal microbiota of infants exposed to IAP through GBS^+ mothers (51). Additional disturbances to the infant microbiota following IAP exposure have been reported out to 90 days of life (48, 52–59) and are reviewed elsewhere (60). GBS may be transmitted to the neonate at low levels during delivery, even with IAP administration, although IAP may reduce the severity of or delay LOD (16). Infants may also be exposed

postpartum through GBS$^+$ breast milk or colonized caregivers (21, 61, 62). It has been hypothesized that a dysbiotic or delayed maturation of the gastrointestinal microbiota may provide a foothold for GBS to initiate LOD (63). This is supported by observations that GBS appears in infant stool prior to LOD but is undetectable in healthy infants (64) and that empirical antibiotic therapy in low-birthweight infants increases the risk of LOD with GBS and other pathogens (65). Furthermore, animal studies comparing neonatal and adult germfree and conventional mice demonstrate increased susceptibility to GBS translocation in the gut in animals with juvenile or absent microbiota (66).

In the context of host-associated viruses, clinical reports of GBS-viral interactions are rare and limited to co-occurrence observations. HIV infection is a risk factor for GBS invasive disease in nonpregnant adults (67, 68). In pregnancy, infants born to HIV$^+$ mothers have increased risk for GBS LOD (69–71), although no differences in maternal colonization between HIV$^+$ and HIV$^-$ women are reported (72–75). This heightened risk may be the result of indirect immune suppression, since HIV$^+$ mothers have lower transplacental transfer of anti-GBS antibodies to their infants than HIV$^-$ controls (76–78). Other associations include increased shedding of herpes simplex virus 2 in women with higher GBS vaginal burdens (79), and a case report of respiratory syncytial virus and GBS coinfection (80). Experimental evidence supports glycan-mediated interactions of GBS with viral pathogens, including influenza virus types A and B, parainfluenza virus, and paramyxoviruses (81–83), and prior exposure to influenza A enhances GBS virulence and adherence *in vitro* and *in vivo* (84–86). Nevertheless, concurrent or subsequent influenza and group B streptococcal lung infections are not reported in the clinical literature. In terms of bacterial viruses, or bacteriophages, most GBS strains (~70 to 85%) contain 1 to 4 prophages, which carry genes associated with defense, stress response, or virulence (87–91). Although not fully characterized, the retention of genetically similar GBS prophages in certain clonal complexes associated with pathogenesis and colonization suggests a beneficial role in host adaption (87, 90, 91).

GBS AND THE ANIMAL MICROBIOTA

While GBS is most notorious for its role in human disease, GBS colonization and/or disease are reported in many animals, including camels (92), cats and dogs (93), dolphins (94), seals (95), crocodiles (96), and fish (97). Although GBS-microbe associations within animals are not well described, there are several studies describing potential interactions between GBS and other resident or therapeutic microbes. GBS colonizes the gastrointestinal tract in 10 to 30% of dairy cattle (98, 99) and is a common and costly agent of mastitis due to reduction in both milk quality and production (100–102). Even subclinical mastitis causes a decrease in milk production and risk of spreading within the herd, which may lead to greater economic losses than clinical mastitis (3). In 16S rRNA amplicon sequencing studies, GBS-induced subclinical mastitis coincides with increased *Streptococcus* abundance (3, 103), although delineation between GBS and other *Streptococcus* species was not determined. Other perturbations to the milk microbiome were inconsistent across studies and include reduced *Acinetobacter*, *Stenotrophomonas*, *Microbacterium*, and *Corynebacterium* (103) or increased *Aeromonas* and *Chryseobacterium* (3) (Table 1 and Table 2). GBS can also cause invasive disease in fish, including Nile tilapia (104) and ya-fish (105). In a live attenuated vaccine study in Nile tilapia, introduction of attenuated GBS strain YM001 temporarily reduced abundance of intestinal *Cetobacterium*, *Romboutsia*, and *Brevinema* and increased that of *Bacteroides* and *Akkermansia*; however, these effects resolved within a week (106). In a continuous-flow competitive exclusion culture system of communities derived from farmed tilapia, GBS-inhibiting activity of community supernatants was positively correlated with *Cetobacterium* and *Plesiomonas* abundance (107). GBS-microbiome interactions that occur within bovine or fish hosts may be also relevant to zoonotic infections. GBS interspecies transmission to humans may occur as a result of raising livestock (108–111) or through consumption of infected fish (112–114). Indeed, the hypervirulent sequence type 17 lineage, significantly

overrepresented in neonatal invasive disease, appears to have recently arisen from a bovine strain (115).

Although not recognized as a common endogenous microbe in laboratory animal species, GBS has been reported in some colonies of mice (116–119) and rats (120, 121). Animal models have also been used to experimentally study GBS-microbe interactions relevant to human colonization and disease. In a mouse model of GBS vaginal colonization, increased GBS uterine ascension was observed in conventional mice with *Staphylococcus*-dominant vaginal microbiota compared to mice harboring other vaginal taxa (122). Additionally, GBS inoculation induced instability of the vaginal microbiota, including early displacement of endogenous *Staphylococcus* spp. (122, 123) (Table 2). The murine gastrointestinal tract has also been implicated in GBS pathology. Murine neonatal susceptibility to GBS invasion of the meninges appears to be mediated by an immature gastrointestinal microbiota, since GBS neuroinvasion can be partially mitigated in neonatal mice by transplantation with adult mouse microbes (66). Furthermore, germfree adult mice have enhanced susceptibility to GBS invasion that can be rescued with microbial transplantation (66), although no particular taxa were associated with increased susceptibility or protection in this study. The murine microbiota has also been studied in the context of testing the impact of GBS therapeutic strategies on the endogenous microbiota in preclinical models. In a GBS vaginal colonization murine model, treatment with human milk oligosaccharides reduced GBS vaginal burdens with minimal changes to the endogenous vaginal microbiota (123). In a study assessing the efficacy of a maternal GBS-specific rGAPDH (recombinant glyceraldehyde-3-phosphate dehydrogenase) vaccine on infant GBS colonization and immune and neurologic development, maternal GBS vaccination resulted in distinct pup fecal microbiota through 90 days of life with an increase in *Enterobacteriaceae* compared to sham controls (124). Of concern, maternal GBS rGAPDH vaccination also was associated with changes in offspring, including altered immune profiles in intestinal and brain tissues combined with aberrant behavior and stress responses (124). Together, these human clinical association studies and preclinical animal models do not reveal large microbial disturbances as a result of GBS colonization as a whole, but rather suggest that GBS may influence cocolonization of individual taxa within the community.

SYNERGISTIC INTERACTIONS WITH GBS AND OTHER MICROBES

GBS and *Staphylococcus aureus*. *Staphylococcus aureus* is a Gram-positive pathobiont that colonizes the skin, nasal passages, and vaginal tract of humans (125, 126). GBS and *Staphylococcus* spp., including *S. aureus*, are often coisolated from the vaginal tract of nonpregnant (32) and pregnant (127–132) women, and both organisms are often associated with reduced *Lactobacillus* and increased incidence of aerobic vaginitis (133, 134) (Table 1). In contrast, several studies have not observed an increased cooccurrence of GBS and *S. aureus* within the vaginal tract (135, 136). Moreover, GBS and *S. aureus* are also coisolated from the nasopharynx in infants (137) and in neonatal blood samples (138). In nonpregnant adult GBS invasive disease, *S. aureus* is the most common co-occurring pathogen in polymicrobial infections, including bacteremia or sepsis (139–142), pneumonia (143), and bone and joint infections (144). Although the underlying mechanisms driving this polymicrobial pathogenesis are unknown, some studies have begun to elucidate GBS-*S. aureus* interactions. Experimental studies show that GBS increases *S. aureus* production of toxic shock syndrome toxin-1 by 3-fold *in vitro* (145) (Fig. 1) and does not inhibit *S. aureus* growth (146–148). Although the synergistic cohemolytic effects of *S. aureus* sphingomyelinase C and GBS CAMP factor have been used for decades in clinical microbiology for definitive diagnosis of GBS (149), the contribution of this enhanced hemolysis to host-microbe interactions remains elusive. GBS CAMP factor is dispensable for GBS virulence and colonization in *in vitro* and *in vivo* models (147, 150), and no differences were found between CAMP-deficient and wild-type GBS interactions with vaginal epithelial cells in the presence of *S. aureus* (147). Since individuals suffering from polymicrobial GBS and *S. aureus* interactions frequently report metabolic and/or immune dysfunction such as diabetes (151), future

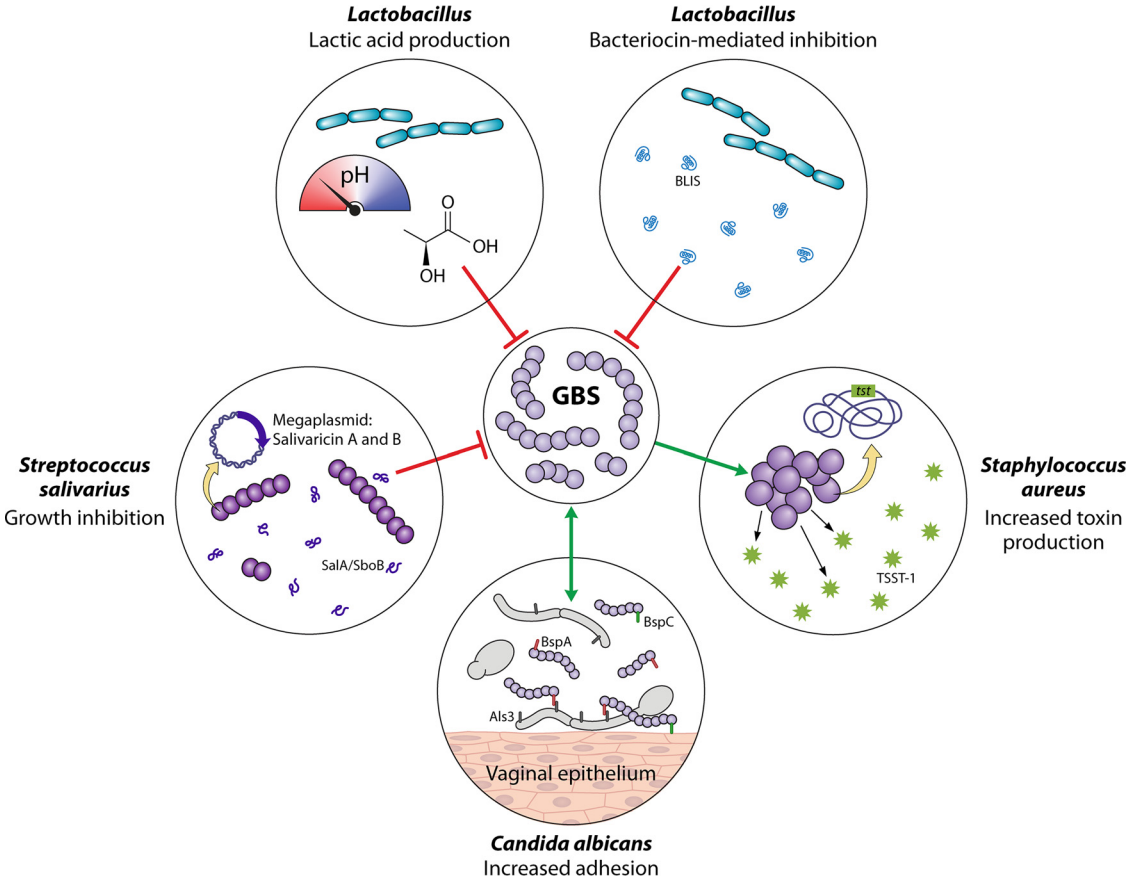

FIG 1 Social network of group B *Streptococcus*: mechanisms of negative (antagonistic) and positive (synergistic) GBS-microbe interactions. The network is ordered clockwise from the lower left. *Streptococcus salivarius* K12 produces salivaricin A and B to inhibit GBS growth *in vitro* and reduce GBS vaginal colonization *in vivo* (206). Lactic acid production by *Lactobacillus* spp. reduces pH and inhibits GBS growth *in vitro* (220, 226, 227). Multiple *Lactobacillus* spp. produce bacteriocin-like inhibitory substances (BLIS) that elicit bactericidal or inhibitory activity. Examples include *L. salivarius* CRL 1328 salivaricin (221), a *L. acidophilus* KS400 bacteriocin (222), an *L. fermentum* CS57 bacteriocin-like substance (218), and synergistic activity of bacteriocins from *L. fermentum* L23 and *L. rhamnosus* L60 (223, 224). GBS antigen I/II family adhesins BspA and BspC facilitate GBS interactions with *Candida albicans*, in part through hypha-specific ALS3, and promote binding of both organisms to the vaginal epithelium (201, 202). GBS supernatant increases *S. aureus* expression of *tst*, the gene encoding toxic shock syndrome toxin-1 (TSST-1), *in vitro* (145).

work should assess GBS-*S. aureus* interactions in the context of host immunity and host and microbial metabolism.

GBS and *E. coli*. Although *E. coli* is an almost universal colonizer of the human gut, the vaginal tract is also a reservoir for commensal *E. coli* strains as well as extraintestinal pathogenic *E. coli* strains, such as those causing urinary tract infection (152) or neonatal sepsis and meningitis (153, 154). Independently, GBS and *E. coli* have similar colonization rates in the maternal vaginal tract (155, 156) and are the two leading causes of infant early-onset sepsis and associated mortality, accounting for 70% of all sepsis cases (157). Although GBS EOD incidence has been reduced with maternal screening and IAP, *E. coli* early-onset sepsis has not been impacted by this intervention, and IAP exposure may be contributing to ampicillin-resistant *E. coli* infections (157–161). GBS and *E. coli* are coisolated from the vaginal tract of pregnant (44) and nonpregnant women (44, 162) in some cohorts, but not others (41, 155) (Table 1). GBS and *E. coli* have also been coisolated from uterine swabs in patients undergoing cesarean sections (163), and rare polymicrobial reproductive tract infections have been reported (164). Although the specific molecular interactions are unknown, vaginal host mediators that inhibit *E. coli* are reduced in individuals colonized by both *E. coli* and GBS (165), and GBS does not inhibit *E. coli* growth *in vitro* (148). Additionally, cross-feeding of metabolites between GBS and *E. coli* has been observed *in vitro* (166). GBS and *E.*

coli may also collude to cause urinary tract infections. Midstream urine samples that test positive for GBS are associated with *E. coli*-positive urine collected via urinary catheter (167). In animal models of urinary tract infection, GBS presence in the bladder increases *E. coli* burdens (168), but it is currently unknown whether this is through direct or indirect mechanisms. GBS capsular sialic acids engage sialic acid-binding immunoglobulin-type lectins (Siglecs) on immune cells to repress activation in multiple cell types, including macrophages and neutrophils (168, 169), which may indirectly permit higher *E. coli* burdens. Future work is needed to characterize the co-occurrence of GBS and pathogenic *E. coli* in the vaginal tract as a precursor to invasive disease such as urinary tract infection or neonatal sepsis.

GBS and *Akkermansia* (including *A. muciniphila*). A fairly newly described species, *Akkermansia muciniphila* (170), has been associated with host gut health and positive health outcomes under a variety of conditions, including obesity (171, 172), resistance to immunotherapy (173), and liver disease (174). A recent analysis of the vaginal microbiota in pregnancy observed increased co-occurrence of GBS and *A. muciniphila* in women that delivered preterm compared to term births (175) (Table 1). In a Nile tilapia study, introduction of an attenuated GBS strain temporarily increased *Akkermansia* from 1% relative abundance to 28% relative abundance in the intestinal tract 3 days after inoculation, although the species of *Akkermansia* was not resolved (106). In murine models, vaginal *A. muciniphila* was identified in GBS-inoculated mice (123, 175), achieving statistically significant coassociation with GBS in one study (175). *In silico* metabolic modeling predicted multiple cross-feeding compounds between GBS and *A. muciniphila*, and a murine model demonstrated prolonged GBS vaginal persistence with coexposure to *A. muciniphila* (175). With recent discoveries of *A. muciniphila* consumption of host-produced substances, including mucin degradation (170, 176), and the importance of mucins in host defense against GBS in the reproductive tract (177), these interactions suggest mutual synergies at the mucosal surface are important for GBS persistence.

GBS and *Prevotella* (including *P. bivia*). *Prevotella* spp. are commonly found in the human vaginal and gastrointestinal tracts (178–180). Increased *Prevotella* species abundance is reported in patients diagnosed with BV (181–183), although the causal role for *Prevotella* spp. in BV has not been established (184). Vaginal *Prevotella* species abundance was significantly higher in cohorts of GBS-positive nonpregnant women (32, 33) and postpartum in women that received IAP for GBS (185). Incongruously, pregnant cohorts show mixed results with both positive (46) and negative (40) correlations of *P. bivia* with GBS (Table 1 and Table 2). These mixed results may in part be due to the inability to delineate specific *Prevotella* species in many of the sequence-based studies. Functionally, the combination of GBS and *P. bivia* resulted in more bacterial invasion of the uterus than either species alone in a rat model of pyometra (186). Reports of GBS and *Prevetolla* interactions outside the female reproductive tract are rare. In one case report, GBS and *P. bivia* were coisolated from a scrotal abscess in a diabetic patient (187). Direct interactions between GBS and *P. bivia* and other *Prevotella* spp. have not been well characterized experimentally and should be addressed in future studies.

GBS and *Gardnerella vaginalis*. While *Gardnerella vaginalis* is considered a common member of the human vaginal microbiota (178), increased abundance of *G. vaginalis* is observed in individuals diagnosed with BV (181, 183, 188). Recent work has identified distinct genetic signatures between *G. vaginalis* isolated from healthy women and those from women with BV (188, 189), suggesting a divergence into strains with enhanced or reduced pathogenic capability (190). Clinical studies reporting GBS and *G. vaginalis* coisolation are rare, and none has identified co-occurrence with GBS and *G. vaginalis* in pregnant women (41, 191). In a murine pregnancy model, coinoculation of GBS and *G. vaginalis* increased the likelihood of identifying both organisms in the maternal uterus and fetal placenta (192) (Table 1 and Table 2). However, *in vitro* results show GBS inhibits *G. vaginalis* growth (146), suggesting that GBS-*Gardnerella* interactions may be more complex than a neutralistic relationship and may depend on the pathogenic potential of each individual strain.

GBS and *Candida albicans*. *Candida albicans* is a frequent opportunistic pathogen of multiple human mucosal surfaces, including the mouth, skin, gut, and urogenital tract. GBS and *C. albicans* are frequently coisolated from the vaginal tract of nonpregnant (44, 193, 194) and pregnant (42, 44, 132, 195–198) women. In a murine model of vaginal colonization, GBS presence in the vaginal tract enhances both fungal burdens and proinflammatory cytokines; however, GBS also suppresses hypha formation through reduced expression of EFG1/Hwp1 and dampens the vaginal mucosal Th17 response (199). In the urinary tract, the presence of *C. albicans* promotes GBS adherence to the bladder epithelium and GBS bladder persistence *in vivo* through a mechanism dependent on *C. albicans* hypha-specific adhesin Als3 (200). Two members of the GBS Bsp adhesion family, BspA and BspC, not only enhance GBS adherence to the vaginal epithelium, but also facilitate *C. albicans* vaginal adherence, in part through binding Als3 (201, 202) (Fig. 1). Other molecular interactions between GBS and *C. albicans* include production of a CAMP-like cohemolytic activity *in vitro* (203). Unlike other *Streptococcus* spp., GBS does not appear to use *Candida* mannan as a nutrient source *in vitro* (204). The mounting clinical evidence supporting GBS and *C. albicans* co-occurrence and emerging molecular interactions compel continued characterization of the interspecies interactions for these two important human opportunistic pathogens.

ANTAGONISTIC INTERACTIONS WITH GBS AND OTHER MICROBES

GBS and other *Streptococcus* spp. The most notable antagonistic interactions that GBS encounters may be with other members of its own species or closely related *Streptococcus* spp. In the majority of clinical samples, only one GBS strain is present (11), although cocolonization with multiple GBS has been reported (205). *In vitro*, GBS strains can inhibit growth of other GBS strains or the growth of other beta-hemolytic *Streptococcus* spp., including group A, C, and G *Streptococcus* spp. (146), although the mechanism for this inhibition is unknown. *Streptococcus salivarius* K12 production of salivaricin A and salivaricin B reduces GBS growth *in vitro*, and *S. salivarius* administration reduces GBS vaginal persistence in a murine model (206) (Table 2 and Fig. 1). GBS can also inhibit the growth of *S. salivarius* ATCC 19258, but this growth advantage can be inverted by addition of galacto-oligosaccharide or galactose (207). Aside from influencing growth, GBS can use short hydrophobic peptide (SHP) signaling pheromones to influence biofilm formation in other *Streptococcus* spp. (208). The impact of this signaling on colonization or pathogenesis is still unknown. Direct interactions may further influence colonization success of either organism. For example, GBS coaggregation with *Streptococcus mutans*, an oral *Streptococcus*, has been observed *in vitro* (209). Understanding how GBS competes with or collaborates with other streptococci is an important facet of developing long-term strategies to modulate GBS colonization at the mucosal surface.

GBS and *Bifidobacterium*. As mentioned previously, maternal IAP to prevent GBS transmission to neonates is associated with changes to both the maternal and infant microbiomes. In particular, *Bifidobacterium* spp. are reduced in infants exposed to IAP (51, 56–59) and this perturbation is proportional to the length of IAP exposure (56). Inverse correlations of *Bifidobacterium* spp. and GBS have also been observed in the murine gut in mice fed high-amylose maize, suggesting interspecies antagonism between these two organisms may occur *in vivo* (118). *In vitro*, GBS growth is inhibited by *Bifidobacterium breve* and *Bifidobacterium longum* subsp. *longum* through secreted products of an unknown type (51) (Table 2). These observations support the development of *Bifidobacterium* spp. as an appealing probiotic intervention in the neonatal period due to the combined risk of GBS late-onset disease in GBS-colonized infants and the beneficial associations of *Bifidobacterium* spp. in the infant gut (210).

GBS and *Lactobacillus*. GBS and *Lactobacillus* spp. are often inversely abundant in the human vaginal tract in nonpregnant (9, 211) and pregnant (41, 191) individuals (Table 2). Additionally, GBS and *Lactobacillus* spp. are inversely associated in the bovine mammary gland, with higher GBS/*Lactobacillus* ratios observed in more severe forms of subclinical mastitis (212). In an experimental murine model, repeated vaginal administration of *L.*

reuteri reduced GBS vaginal colonization, suggesting a potential causative effect (213). These inverse associations may be in part due to competition for the same geographic niche within the host, depending on the tissue or organ. While *Lactobacillus gasseri* facilitates GBS association with decidualized human endometrial stromal cells (214), *Lactobacillus acidophilus*, *Lactobacillus paracasei*, and *L. gasseri* reduce GBS adherence to vaginal epithelial cells *in vitro* (215, 216). Direct antagonism is another potential explanation of GBS and *Lactobacillus* species inverse correlations. *Lactobacillus* spp. inhibit GBS growth (214, 217–220) and biofilm formation *in vitro* (214). Examples of *Lactobacillus*-produced products with inhibitory activity toward GBS include *L. salivarius* class IIb bacteriocin salivaricin CRL 1328 (221), an *L. acidophilus* bacteriocin (222), a bacteriocin-like substance in *Lactobacillus fermentum* CS57 (218), synergistic activity of bacteriocins from *L. fermentum* and *Lactobacillus rhamnosus* (223, 224), biosurfactant production by *L. paracasei* (225), and *Lactobacillus* species production of lactic acid since pH neutralization removes GBS inhibitory activity (220, 226, 227) (Fig. 1). Additionally, nonproteinaceous but cell-contact-dependent inhibitory effects have been reported (220). *Lactobacillus* production of another antimicrobial substance, hydrogen peroxide, does not correlate with GBS inhibition (227). Indeed, GBS appears equipped to neutralize both acid and oxidative stress from *Lactobacillus* spp., in part through expression of a pH-regulated NRAMP Mn^{2+}/Fe^{2+} transporter, MntH (228), an NADH peroxidase (229), a superoxide dismutase, SodA (230), and a glutathione synthase (231). One *in vitro* study found that multiple *Lactobacillus* spp. could coaggregate with GBS and enhanced GBS binding to mucin (232), while other studies have not noted GBS-*Lactobacillus* coaggregation (219). Additionally, GBS may counter with its own antimicrobial activity since GBS inhibition of *Lactobacillus* growth has been reported *in vitro* (146, 217). The robust clinical and experimental evidence supporting *Lactobacillus* species and GBS antagonism and the importance of *Lactobacillus* in supporting a healthy vaginal mucosa compel the continuing search for and refinement of *Lactobacillus*-based approaches to control GBS vaginal colonization.

PERSPECTIVES ON THERAPEUTIC DEVELOPMENT

GBS-microbe interactions in susceptible hosts. While frequently isolated from the healthy adult gastrointestinal or vaginal tract in 1 in 5 individuals, the vast majority of GBS invasive disease is borne by specific subsets of the human population, including newborns, pregnant women, the elderly, and immune-comprised individuals, such as those with diabetes. While it is paramount to understand GBS-microbe interactions in those most at risk for GBS invasive disease, there is a paucity of clinical and experimental data from these susceptible populations. Clinical data suggest that GBS blooms in the neonatal gut prior to GBS LOD (64), but the dynamics of the gut microbiota during this process are unknown. Coinciding with the susceptibility window to GBS LOD, the neonatal gut microbiota displays lower α diversity during the first few months of life than at older ages (233). On the other side of the human life span, increased GBS colonization in elderly individuals has been observed in some studies (234), but not others (235–237). Elderly populations show higher incidence of GBS invasive disease and all-cause mortality following GBS infection than younger groups (5, 237–241). Changes to the aging gut microbiota vary across cohorts, which may be attributed in part to subject demographics, comorbidities/medications, and living conditions, but tend to include increased α diversity with age, increased relative abundance of *Akkermansia* and *Escherichia*, and decreased relative abundance of *Faecalibacterium*, *Prevotella*, and *Bacteroides* (242). It is currently unknown whether these changes to the elderly microbiota create a more favorable environment for GBS colonization or invasion of host tissues. Other age-associated conditions may be aggravated by GBS colonization. In a study of postmenopausal women, CST IV-A, a CST with enriched GBS colonization, is associated with mild to moderate vulvovaginal atrophy, although no individual taxa were associated with clinical findings in this study (243).

Diabetes mellitus is consistently identified as a risk factor for GBS invasive disease in nonpregnant adults (4, 67, 139, 237–239, 244–250) and pregnant adults (251), and

significantly increased rates of GBS rectovaginal colonization in diabetic individuals have been observed in some studies (251–259), but not others (234, 260–269). Clinical studies demonstrate alterations to the gastrointestinal microbiota in diabetic individuals, which include increased relative abundance of *Ruminococcus*, *Fusobacterium*, and *Blautia* and decreased relative abundance of *Bifidobacterium* and *Bacteroides* (270). Vaginal microbiome studies, although rarer, report differences in pregnant diabetic individuals, including altered α and β diversity and differential abundance of taxa, but findings were not consistent between cohorts (271, 272). There have been few experimental model studies on GBS in diabetic hosts to date, including GBS invasive disease (119, 273–275), urinary tract infection (276), or diabetic wound infection (277), but it is not yet clear whether diabetic-induced perturbation of the host microbiota facilitates enhanced susceptibility to GBS colonization and infection. To develop tailored therapies for the most susceptible populations, it is important to consider host immune and metabolic factors shaping the microbiota and influencing colonization by opportunistic pathogens, including GBS.

Emerging and future therapeutic avenues. Due to the abundance of *in vitro* observations supporting *Lactobacillus* species inhibition of GBS growth, many clinical studies examining probiotics to control GBS have incorporated *Lactobacillus* spp. Unfortunately, most studies to date report null or mixed results and many are underpowered pilot studies. Four studies have evaluated an oral probiotic combination of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 intervention on GBS colonization during pregnancy. Ho et al. observed a significant decrease of GBS colonization in the intervention group compared to the placebo group (278) (Table 2). Although no differences in GBS colonization prevalence were observed in the second study by Liu et al., potentially beneficial effects such as reduced antibiotic use, reduced incidence of premature rupture of membranes, and decreased GBS abundances by sequencing were reported in the probiotic intervention group compared to the nonintervention group (279). In the third and fourth studies, no differences between the intervention and placebo groups were observed and additional challenges in enrollment and compliance were reported (280, 281). Several other probiotic formulations have been tested, but the routes and lengths of probiotic administration vary across studies. Oral administration of Florajen3 (*L. acidophilus*, *Bifidobacterium lactis*, and *Bifidobacterium longum*) from week 28 of pregnancy to labor onset did not impact GBS clearance in pregnant women in two separate cohorts (282, 283). Oral administration of *L. salivarius* CECT 9145 from weeks 26 to 38 of pregnancy significantly increased GBS clearance from rectal and vaginal samples from GBS^+ women compared to placebo-treated GBS^+ women, and reduced GBS burdens over time were observed in women who remained colonized during probiotic treatment (284). A clinical trial with *L. rhamnosus* HN001 has listed maternal GBS colonization as a secondary outcome; however, results related to GBS colonization from this cohort have not yet been reported (285). A proprietary *Enterococcus faecium*-based probiotic tested in pregnant women resulted in a 6% decreased GBS colonization rate (286). Local vaginal application of *L. plantarum* did not reduce GBS vaginal colonization in a placebo-controlled, double-blind study of nonpregnant women (9). Finally, in a study testing the combination of *Lactobacillus jensenii*, *L. crispatus*, *L. rhamnosus*, and *L. gasseri* as a twice-daily oral probiotic for 14 days beginning at 33 to 37 weeks of pregnancy, no differences in GBS colonization rates were observed between intervention and placebo groups (287). A clinical trial investigating the combination of *L. rhamnosus*, *L. reuteri*, and *S. salivarius* K12 on GBS colonization at delivery as a primary outcome is actively recruiting (288). Bacteriophages or their products are also of interest as a targeted therapy to control GBS colonization and/or disease. Bacteriophage lysins display *in vitro* lytic activity toward GBS, and administration reduces GBS vaginal colonization and lethality *in vivo* (89, 289–294). Maternal GBS colonization rates vary across regions (6, 7), as do burdens of invasive GBS disease (295, 296). While the contribution of GBS-microbe dynamics to regional variation is currently

unknown, this is certainly a point to consider for microbe-based GBS therapy development and implementation.

Another active area of probiotic research for GBS is in the context of preventing invasive disease in the aquaculture setting. One study found that probiotic feeding of *E. faecium* reduced GBS mortality in Nile tilapia, but this effect appears to be independent of the microbiota since *E. faecium* treatment did not alter the fish gut microbiome profile (297) (Table 2). Another probiotic study found treatment with either *L. rhamnosus*, *Lactococcus lactis* subsp. *lactis*, or a combination of the two protected against GBS lethal infection and correlated with an increased intestinal abundance of *Proteobacteria*, including *Escherichia-Shigella* spp. and *Achromobacter* spp. (298). Several other studies have identified probiotics that reduce GBS mortality and modulate the host microbiota in tilapia: Li et al. found that dietary *Clostridium butyricum* was accompanied by decreased abundance of *Cetobacterium* spp. and an increase in *Bacillis* spp. (299), and Xia et al. found that treatment with *Bacillus cereus* was accompanied by a decrease in abundance of *Cetobacterium* and an increase in *Rhizobium* (300). Prebiotic approaches may also have potential impacts on GBS colonization or infection. Feeding woody forages to tilapia encouraged the growth of several organisms, including *Bacillus* spp., which demonstrate antagonistic activity toward GBS *in vitro* (301). In coculture studies with GBS and *S. salivarius*, addition of either galacto-oligosaccharide or galactose inhibited GBS growth (207). Based on the recent surge in probiotic and prebiotic interest in preventing GBS invasive disease in humans and animals, widespread use of microbe-based therapies for GBS may be on the near horizon.

CONCLUSIONS

The diversity of environments that GBS adapts to, from the nares of a camel (92) to the mammary gland of a dairy cow (102), from the maternal vaginal tract (6) to the gut of an infant (64), all of which have distinct resident microbes, implies that GBS has developed numerous microbial interactions that are either synergistic or antagonistic in nature. One major challenge in advancing our understanding of these interspecies interactions is, although there are many clinical studies reporting incidence of GBS and other pathobionts, more often than not, co-occurrences of GBS and these other organisms within subjects are not reported. Future GBS research, in both clinical and experimental settings, should endeavor to address the other microbes present or absent at the host site of interest across the full range of susceptible populations from the newborn to the elderly. Incorporation of new experimental models to study GBS interactions with complex microbial communities *in vitro* (107, 302) or in humanized microbiota animal models *in vivo* (303) may provide a clearer picture of GBS-microbe interactions with translational value. Several recent discoveries provide opportunities to describe GBS-microbe-host interactions with further mechanistic insight, including identification of a GBS type 7 secretion system and its heterogeneous potential toxin and immunity effectors (304, 305) and identification of GBS regulatory factors, such as the two-component system SaeRS, that sense the host environment to drive transcriptional adaptions (306). Finally, recognition of the ability of GBS to acquire nutrients within the host environment, such as degradation of physiologically relevant carbohydrates, including glycogen (307, 308) or fructose (309), provides a starting point for understanding GBS metabolism within the host and in competition with other microbes. If prebiotic/probiotic-based therapies are going to be perfected and implemented, we need to identify microbes that can outfight, outbind, and/or outeat GBS within the host niche.

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