

# Understanding Factors in Group B Streptococcus Late-Onset Disease

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**Abstract:** Group B streptococcus (GBS) infection remains a leading cause of sepsis, pneumonia, and meningitis in infants. Rates of GBS early onset disease have declined following the widespread use of intrapartum antibiotic prophylaxis; hence, late-onset infections (LOGBS) are currently a common presentation of neonatal GBS disease. The pathogenesis, mode of transmission, and risk factors associated with LOGBS are unclear, which interfere with effective prevention efforts. GBS may be transmitted from the mother to the infant at the time of delivery or during the postpartum period via contaminated breast milk, or as nosocomial or community-acquired infection. Maternal GBS colonization, prematurity, young maternal age, HIV exposure, and ethnicity (Black) are identified as risk factors for LOGBS disease; however, further studies are necessary to confirm additional risk factors, if any, for the implementation of effective prevention strategies. This narrative review discusses current and previous studies that have reported LOGBS. Few well-designed studies have described this condition; therefore, reliable assessment of maternal GBS colonization, breastfeeding, and twin delivery as risk factors for LOGBS remains limited.

**Keywords:** neonatal sepsis, prevention, infant, meningitis, CC17

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## Introduction

Group B streptococcus (GBS or *Streptococcus agalactiae*), a gram-positive pathogen that belongs to the Lancefield group B class of streptococci, is a common gastrointestinal and urogenital commensal in adults, which may occasionally precipitate life-threatening infections in neonates, pregnant women, elderly individuals, or in adults with comorbidities.<sup>1,2</sup> GBS colonizes the vagina or vaginal/rectal (VR) sites in 10–30% of pregnant women and frequently causes urinary tract infections, chorioamnionitis, and postpartum endometritis. GBS is also associated with poor pregnancy outcomes, including spontaneous abortion, stillbirth, and preterm birth.<sup>1,3,4</sup>

Since the 1970s, GBS has emerged as a leading cause of sepsis, pneumonia, and meningitis in infants in the USA.<sup>1</sup> The worldwide burden of GBS infection remains significant,<sup>5</sup> and GBS affects approximately 320,000 neonates (90,000 of which die) across low-, middle-, and high-income countries.<sup>6</sup> GBS infections significantly contribute to the global pediatric mortality rates (children aged <5 years), with the highest rates observed in low-income countries.<sup>7</sup> Studies performed since the 1970s have identified maternal VR carriage as a primary risk factor (RF) for neonatal

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colonization and infection,<sup>8–14</sup> and research has focused on strategies to prevent mother-to-infant transmission.<sup>15–17</sup>

Neonatal GBS infections are categorized into early-onset disease (EOGBS, presenting at 0–6 days of life) and late-onset disease (LOGBS, presenting at 7–90 days of life).<sup>3</sup> GBS infections may occur beyond 90 days and within 6 months of life (ultra-late onset disease [ULOGBS]). Cohort studies have shown that LOGBS and ULOGBS are identical clinical and bacteriological entities, except for prematurity, which is more commonly associated with ULOGBS.<sup>18</sup> We focus on LOGBS; therefore, ULOGBS is not discussed in this review.

Early studies report that the rates of EOGBS disease were approximately 4-fold higher than those of LOGBS. Clinical trials performed since the 1980s report that administration of intravenous ampicillin or penicillin (intrapartum antibiotic prophylaxis [IAP]) to mothers at a high risk of GBS transmission to their newborn could effectively prevent EOGBS. IAP has significantly reduced the rates of EOGBS;<sup>3</sup> the incidence of EOGBS in the USA was as high as 5 cases per 1000 live births prior to the widespread availability of IAP<sup>19</sup> and has declined significantly post-IAP, with the trend continuing even in recent years (0.37/1000 live births in 2006 and 0.23/1000 live births in 2015). The LOGBS rates among infants have stabilized in the USA (mean 0.31/1000 live births) and are now higher than those of EOGBS.<sup>20</sup> Therefore, investigation of RFs associated with LOGBS is important because in some high income countries LOGBS is now the most common presentation of neonatal GBS disease.

## Pathogenesis and Clinical Presentation of Early- and Late-Onset Group

### B Streptococcal Disease

EOGBS and LOGBS are similar with regard to bacterial attachment to the epithelial surface, invasion, and bacteremia and differ only with regard to the timing and mode of exposure. EOGBS and LOGBS differ in their clinical presentation, mortality, morbidity, epidemiological characteristics, and percentage of GBS serotypes that cause invasive infections. The route of transmission of GBS in EOGBS is well known, whereas that in LOGBS remains unclear. EOGBS is vertically acquired, and maternal anogenital colonization is a prerequisite in such cases. Neonatal exposure occurs in utero (hours or a few days before birth) or during passage through the birth canal. Before birth, GBS are aspirated into the lungs (exposure of

the respiratory epithelial surface) with subsequent invasion of pulmonary vessels. Aspiration and swallowing of vaginal secretions result in bacterial adherence to respiratory and gastrointestinal mucous membranes with subsequent bacterial invasion of the bloodstream,<sup>1</sup> and infants typically present with pneumonia or sepsis at birth or soon thereafter.<sup>1,8</sup> In contrast, LOGBS can result from mucosal colonization of GBS at the time of delivery or postpartum, from the mother or from other sources. Early studies indicate that approximately 40% of neonates with GBS colonization at birth continue to show intestinal colonization even at 12 weeks of life and that intestinal GBS colonization is an important precursor of LOGBS.<sup>14,21</sup> Studies in animal models have shown that oral administration of GBS leads to systemic disease.<sup>22</sup> The pathogenesis of LOGBS involves GBS adhesion to mucosal surfaces, followed by invasion of the epithelium and subsequently the bloodstream. Factors that mediate persistent intestinal colonization or promote the shift from intestinal colonization to invasive GBS disease remain unknown. A recent study by Vaz et al in a murine model with exposed offspring and juvenile mice reported the kinetics of gastrointestinal colonization by GBS, progression to invasive disease, and the role of GBS-specific immunoglobulin (Ig)G production. The experimental animals showed prolonged gastrointestinal colonization and developed invasive disease, following both perinatal (21% of cases) and postnatal exposure to GBS (27% of cases).<sup>23</sup>

Breast milk is considered a possible source of LOGBS and may account for sustained transmission of GBS to the newborn with consequent promotion of gut translocation and LOGBS.<sup>24</sup> However, whether breast milk is only a marker for high levels of neonatal nasopharyngeal GBS colonization is unclear.<sup>2,24–26</sup>

LOGBS can be also transmitted from non-maternal sources (such as from caregivers); it is shown that all cases of LOGBS are not necessarily associated with maternal colonization.<sup>27,28</sup> Nosocomial GBS transmission through healthcare workers was more common some decades earlier when post-parturient mothers and infants typically remained in the hospital  $\geq 1$  week.<sup>11,29,30</sup> However, currently full- or late-preterm neonates remain in the hospital only for a few days and “room in” with their mothers; therefore, predominant routes of transmission may have changed lately. Nosocomial GBS transmission in neonatal intensive care units (NICUs) is perhaps more common than expected. Two-year surveillance of all LOGBS cases in an NICU in the UK with serotyping and genome

sequencing of GBS isolates together with neonatal rectal screening<sup>31</sup> showed four clusters with 12 LOGBS cases, of which 11 were associated with at least one other LOGBS isolate. The authors concluded that even a single NICU case should be considered secondary to potential nosocomial transmission. LOGBS sepsis warrants prompt investigation and improved efforts for prevention of infection and prompt treatment because it may not necessarily indicate a sporadic occurrence. Hospital clusters of invasive GBS infections were investigated in a recent systematic review; crowding, inadequate disinfection of equipment and surfaces, unsatisfactory practices for prevention of infection, or a high patient-to-nurse ratio were implicated in the occurrence of LOGBS clusters.<sup>32</sup>

Usually, LOGBS presents a wider clinical spectrum than EOGBS and commonly manifests with bacteremia without an apparent focus of infection. Meningitis is significantly more frequent in LOGBS than in EOGBS (31% vs 9% of cases)<sup>33,34</sup> and may result in long-term neurodevelopmental sequelae of variable severity in up to 50%<sup>35</sup> and moderate-to-severe neurodevelopmental impairment in approximately 23% (95% confidence interval [CI] 19–26%) of survivors.<sup>36</sup> LOGBS rarely affects bones, joints, soft tissue, or the urinary tract (focal infections).<sup>1,33</sup> Facial cellulitis and adenitis localized to the submandibular or parotid region are known to occur, and these infections are attributed to breastfeeding.<sup>37</sup>

In the absence of intervention, the gastrointestinal and/or upper respiratory tracts of approximately 29–85% (mean 50%) of neonates born to GBS carrier mothers show colonization at birth. Most infants remain healthy, but 1–2% of the exposed neonates develop EOGBS. IAP prevents EOGBS and greatly reduces neonatal colonization at birth.<sup>38–42</sup> Reportedly, GBS colonization of mucous surfaces occurs at the time of delivery in some infants who develop LOGBS. In a seminal study, Dillon reported that approximately 50% of infants with LOGBS showed colonization at birth with the same GBS serotype as the mother.<sup>14</sup> However, whether this route of LOGBS transmission is common in real-world practice is unclear, particularly after the widespread use of IAP as a standard of care, which interrupts mother-to-infant transmission. IAP does not eradicate GBS carriage, and mothers remain a source of GBS transmission during the postpartum period.<sup>25,28</sup>

IAP does not affect the LOGBS rates; however, it may delay the time of onset of LOGBS or reduce its severity. An Italian prospective cohort study that investigated 100

cases of LOGBS between 2003 and 2010 reported that infants who received IAP for any length of time were more likely to be older at the time of LOGBS presentation (median age at symptom onset 40.0 days, interquartile range [IQR] 25.0–62.0) than those who did not receive IAP (median age at symptom onset 24.0 days, IQR 15.0–41.0, odds ratio [OR] for early presentation 4.3, 95% CI 1.7–10.8,  $p < 0.01$ ).<sup>27</sup> IAP exposure was significantly associated with mild rather than severe LOGBS ( $p = 0.03$ ); however, the mechanisms underlying this association remain unclear. The severity of LOGBS is usually higher during the first few weeks of life; therefore, IAP may modify the routes of GBS transmission (from vertical to horizontal), with a consequent delay in disease onset and reduced disease severity. The unchanged rates of LOGBS following the widespread use of IAP support the role of postpartum colonization from maternal or non-maternal sources.<sup>27</sup>

## Microbiological Aspects

Ten immunologically distinct serotypes of GBS have been defined based on surface polysaccharides (Ia, Ib, II to IX). A systematic review and meta-analysis that included approximately 6500 strains obtained from neonatal GBS disease isolated worldwide between 2000 and 2017 observed that five serotypes (Ia, Ib, II, III, and V) account for >97% of all cases of this disease.<sup>43</sup> Serotype III strains are clinically the most important and account for approximately 50% of EOGBS and are the predominant strains in cases of LOGBS, with infection rates of >70%.<sup>44–47</sup> The predominance of serotype III is primarily attributable to the prevalence of a single clonal lineage defined as Clonal Complex 17 (CC17), transmitted worldwide.<sup>48–50</sup> The monoclonal GBS nature of LOGBS etiology remains unexplained.

Maternal GBS colonization is the principal risk factor for LOGBS. Longitudinal studies during the postpartum period have shown that delayed GBS colonization occurs in infants born to GBS carrier mothers who receive IAP.<sup>51</sup> Approximately 20% of neonates show colonization 1 month after birth with >95% concordance between the maternal and infant GBS type.<sup>25,28,51</sup> The distribution of GBS serotypes in colonized mother-neonate pairs resembles that of carriage observed during antenatal screening; serotype III-CC17 is detected but is not the exclusive serotype identified.<sup>25</sup>

A recent study reported that compared with non-CC17, the CC17 strain is not associated with increased mother-to-

child transmission during delivery, and no specific factor was correlated with CC17 colonization in infants, compared with other GBS types. Nevertheless, new GBS colonization that occurs in neonates between 21 and 60 days after birth is more frequently caused by CC17 as opposed to non-CC17 strains.<sup>28</sup>

Meningeal tropism and propensity to cause meningitis (which is the most common clinical presentation of LOGBS) are attributable to the peculiar virulence traits of CC17 GBS. Compared with non-CC17 strains, CC17 GBS strains possess the exclusive surface adhesins, HvgA and Srr2, which promote increased binding to brain endothelial cells. While the molecular ligand of HvgA remains unidentified, a recent study has shown that Srr2 binds to integrins  $\alpha 5\beta 1$  and  $\alpha v\beta 3$ , which contribute to bacterial adhesion and invasion of brain endothelial cells and passage across the brain-blood barrier. Expression of these integrins is higher in neonatal than in adult brain vessels, which accounts for the greater tendency of CC17 to cause neurotropic disease in neonates with LOGBS.<sup>52</sup>

Comprehensive genomic analysis of 626 CC17 isolates obtained worldwide between 1955 and 2016 to determine the underlying differences between carriage and disease-associated GBS strains showed that frequent mutations in the sensor protein of the regulatory transcriptional system CovS/R and in the serine/threonine-specific protein kinase were distinctive features of disease-specific CC17 isolates, which highlights the crucial role of fine-tuning of transcription and expression of virulence factors to modulate the pathogenicity of GBS.<sup>53</sup> Parallel and convergent evolution (homoplastic events) were observed in other virulence components, such as in the capsule biosynthesis operon, the pilus, and surface protein Rib, which reflects the progressive temporal adaptation of CC17 GBS strains to host immune pressure. Among the alpha-like protein (Alp) members, a family of important adhesins detected in nearly all GBS strains,<sup>54</sup> serotype III strains contain only the Rib variant, which reportedly is an important contributor to the virulence of the organism and to the development of protective immunity. Comparison of carriage-related isolates with disease-associated strains has sometimes shown a significant reduction in the number of tandem repeat units (which constitute the internal portion of Rib) in strains from neonatal infections, which modulate its exposure on the bacterial surface.<sup>55–57</sup> The phase variation in the Alp proteins depends on their highly immunogenic properties, which are inversely correlated with the number of their repeated domains.<sup>55,56</sup> Therefore, a smaller Rib enables

serotype III CC-17 strains to easily escape the maternally transmitted antibodies and to be strongly selected in the course of disease. This confers a selective advantage in neonatal disease following maternal transmission.<sup>58</sup>

The success of CC17 is gaining much attention with recent reports on the emergence of a multidrug resistant (MDR) CC17 sub-clone.<sup>59–62</sup> The GBS type III MDR CC17 sub-clone possesses integrative and conjugative elements (ICE) that confer additional genetic resistance to tetracycline, macrolides, and lincosamides and also high-level resistance to streptomycin and kanamycin.<sup>59</sup> Genomic studies have shown that the ICE elements replace the 16 Kb genome region that comprises the entire pathogenicity island encoding pilus 1.<sup>59,60</sup> Currently, two variants of ICE have been identified; these show a mosaic structure with modules derived from *S. suis*, *S. dysgalactiae*, *S. pyogenes*, and *S. pneumoniae*.<sup>59</sup> The MDR CC17 sub-clone was firstly reported from the analysis of genomic GBS CC17 strains isolated from neonatal infections in Southern China in 2013–2014 (riferimento di Campisi). Nevertheless, retrospective analyses demonstrated that it has been circulating in Canada,<sup>60</sup> as well as in Portugal<sup>61</sup> and France<sup>62</sup> since the year 2010.

Data from the surveillance network in France show a sustained increase in the incidence of LOGBS, with an overall 65% higher incidence over the past 20 years, along with an increase in prevalence of the hypervirulent CC17 GBS clone and its MDR sub-lineage in LOGBS. Specifically, the amikacin resistance rate among GBS strains from neonatal disease increased from 0% in 2007 to 18% in 2019, and the percentage of LOGBS infections caused by the MDR CC17 sub-clone was approximately 14% in 2019.<sup>62</sup>

Despite the availability of effective drugs, such as beta-lactams against GBS infections, the high plasticity of the mobile genetic elements that possess multiple antibiotic resistance genes in GBS type III CC17 MDR sub-clones is a significant concern for possible therapeutic failures, particularly in hospital settings such as in NICUs that are associated with extensive antibiotic use. Prolonged hospitalization predisposes neonates, particularly premature newborns to infection, with a high risk of horizontal GBS transmission and LOGBS.

## Risk Factors for Late-Onset Group B Streptococcus Disease

RFs for LOGBS remain quite indeterminate; however, evidence from cohort and case-control studies indicates

that ethnicity, prematurity, maternal GBS colonization, young maternal age, and HIV infection serve as RFs for LOGBS. Case reports or small case series have also implicated breast milk and twin delivery as RFs; however, published data do not support this view. We describe known and presumed RFs for LOGBS. **Table 1** summarizes proven or suspected RFs and potential strategies (when available) to prevent LOGBS. However, maternal vaccination would prevent the largest number of LOGBS cases, according to vaccine efficacy and coverage in pregnant women. The hypothetical estimates of protection following maternal vaccination are reported in a recent systematic review.<sup>6</sup> Unfortunately, no vaccination strategy will prevent LOGBS in very preterm neonates, since the transplacental transmission of maternal protective IgG antibodies mainly occurs after 34 weeks' gestation.

**Table 1** Proven or Suspected Risk Factors for Group B Streptococcus Late-Onset Disease and Potential Strategies for Its Prevention

Risk Factors	Potential Strategy for Preventing
Ethnicity	NA
Prematurity	Prevention of maternal diseases that can potentially lead to preterm birth (obesity, hypertension, diabetes, heart disease, others) Prevention of inadequate lifestyles, which increase the risk of preterm birth Prevention of healthcare associated infections among in hospital premature neonates
Maternal group B streptococcus colonization	Maternal vaccination (possible prevention of maternal group B streptococcus colonization) Prevention of mucous neonatal colonization (hygiene measures, ie hand washing)
Young maternal age	NA
Exposure to the human immunodeficiency virus	Prevention of sexual transmission of HIV in adults
Breastfeeding	Prevention of maternal mastitis
Twin delivery	Prevention of twin deliveries, i.e.those associated with assisted fertilization

**Abbreviations:** NA, not applicable; LOGBS, group B streptococcus late-onset disease.

## Ethnicity

Cohort studies (mostly performed in the USA) have shown significant racial differences associated with LOGBS and that it affects a disproportionately high percentage of Black infants. GBS surveillance performed between 1999 and 2005 across 10 states that participated in the Active Bacterial Core surveillance/Emerging Infections Program Network in the USA reported that among 1036 patients with LOGBS, 28% were Black and the overall incidence of LOGBS among the Black population was 2-fold higher than that among the White population (relative risk [RR] 2.0, 95% CI 1.8–2.2).<sup>63</sup> The correlation between race and prematurity, birth weight, maternal age, adequacy of prenatal care, or socioeconomic status could not be established, although socioeconomic status was not measured accurately.<sup>63</sup> Schuchat et al<sup>64</sup> retrospectively investigated 71 and 37 infants with invasive EOGBS and LOGBS, respectively, between 1982 and 1983 in Atlanta. Univariate analysis showed that 78% of LOGBS occurred in Black infants, independent of additional RFs. Multivariate analysis showed that Black ethnicity was strongly and independently associated with LOGBS (RR 35.1, CI 4.7–266.0). Nanduri et al<sup>20</sup> investigated 1387 patients with LOGBS, based on active population-based and laboratory-based surveillance of invasive GBS disease (performed through Active Bacterial Core surveillance in the USA between 2006 and 2015); 588 infants (42.4%) were Black, 706 (50.9%) were White, and the remaining 94 (6.8%) belonged to other races. Annual LOGBS incidence rates were higher in Black than in White infants (mean [range] rate ratio 2.9, CI 1.9–4.4 times).<sup>20</sup> Lin et al<sup>65</sup> investigated the RFs for LOGBS (disease onset or first positive culture between 7 and 180 days after birth) in the greater Houston area (1995–2000). These authors compared 122 infants with 122 controls matched for birth hospital and date of birth and observed that 50% of the infants were preterm, and 84% of these infants were born at  $\geq 34$  weeks of gestation. The risk for LOGBS increased by 3.70 (95% CI 1.35–10.1) in infants born to Black mothers. Although such disparities have reduced in recent decades, they are known to occur. In contrast, a reduced temporal trend in LOGBS was reported in Tennessee between 2009 and 2018. A study that investigated 359 infants with GBS disease (0–90 days of life) reported that 214 were diagnosed with LOGBS. The LOGBS rates among Black infants have shown a reduced temporal trend (RR 0.90, 95% CI 0.84–

0.97,  $p=0.003$ ); however, no changes were observed among White infants (RR 0.99, 95% CI 0.92–1.07,  $p=0.768$ ).<sup>66</sup>

## Prematurity

LOGBS disproportionately affects premature neonates.<sup>2</sup> Cohort and case-control studies have shown an increased risk of LOGBS in preterm infants,<sup>20,27,65</sup> although a gradient showing an increased risk associated with decreasing gestational age is not clearly defined. The increased risk of LOGBS in preterm neonates is mainly attributable to their immature immune system, which cannot mount an adequate immune response against GBS; placental transfer of specific maternal IgG antibodies usually occurs during late pregnancy (serum levels of GBS type-specific antibodies increase to 75–80% of the maternal levels from 34 weeks of gestation, and levels before 34 weeks of gestation are only 20% of the maternal levels).<sup>67</sup> Furthermore, survival of extremely preterm neonates has improved in recent times; an abnormal intestinal flora<sup>68</sup> associated with repeated antibiotic courses and prolonged hospital stay predisposes these neonates to nosocomial pathogen transmission.<sup>32,69,70</sup>

Jordan et al<sup>71</sup> investigated 1726 patients with LOGBS in an active, population-based surveillance study performed across 10 states in the USA (between 1990 and 2005) and observed that although gestational age was known only in 455 of the 1726 patients, the rate of preterm neonates born before 37 weeks of gestation was high at 49%. An Italian area-based study reported that preterm neonates accounted for approximately 33% of all cases of LOGBS, and an approximately 16-fold increase in incidence rates was observed in preterm neonates born before 34 weeks of gestation than in full-term neonates (incidence rates 3.8 and 0.24/1000 live births, respectively).<sup>27</sup> A recent study (between 2006 and 2015) by Nanduri et al reported from the Active Bacterial Core surveillance in the USA observed that approximately 40% of LOGBS cases occurred in infants born before 37 weeks' gestation, and the incidence of LOGBS was 6-fold higher in preterm than in full-term infants.<sup>20</sup> Furthermore, mortality rates were disproportionately higher among preterm neonates (LOGBS case-fatality rates 3.4% and 7.8% among full-term and preterm infants, respectively). However, case-control studies may more accurately define the increased risk of LOGBS. Lin et al<sup>65</sup> observed that each week of decreasing gestation was associated with an increased risk by a factor of 1.34. Similarly, Pintye et al<sup>72</sup> reported a case-control study on RFs in 138

infants with LOGBS, which occurred before and after the implementation of universal screening and IAP. These authors investigated infants born in Washington State between 1992 and 2011, who were re-hospitalized between 7 and 89 days of life with a diagnosis of LOGBS (identified by the International Classification of Diseases-9 codes) and observed that each week of decreasing gestation was associated with an increased risk of LOGBS by a factor of 1.24.

## Maternal Group B Streptococcus Colonization

Maternal GBS colonization is an important RF for LOGBS and is probably the main RF in full-term neonates, who usually have frequent and close contact with their mothers after discharge from the nursery. In contrast, preterm neonates admitted to hospitals are less frequently in close contact with their mothers and therefore they show a lower risk of maternal postpartum transmission of GBS; however, these neonates show a high risk of nosocomial infections, including GBS.<sup>73</sup>

In a prospective cohort study performed between 1977 and 1983, which included 50 infants with invasive GBS infection, 21 of 45 infants developed LOGBS. Maternal carriage with the same GBS serotype that caused LOGBS was detected at the time of delivery in 10 (48%) of 21 mothers.<sup>14</sup> Despite the small sample size of the study, maternal colonization rates were approximately 2-fold higher than those usually observed in pregnant women at VR sites. More recent studies have shown that prenatal colonization rates in mothers who deliver neonates with LOGBS are similar or moderately higher than those usually observed in pregnant women. An active, population-based surveillance study performed across 10 states in the USA (between 1990 and 2005) investigated 1726 infants with LOGBS and observed that only 182 women had documented results of prenatal GBS screening and 83 (46%) showed positive results for GBS colonization.<sup>71</sup> A French cohort study reported 438 GBS neonatal invasive infections (between January 2007 and December 2012), of which 264 were diagnosed as LOGBS. Among 102 mothers who underwent prenatal vaginal GBS screening, 32 (31%) showed GBS colonization. Maternal VR colonization rates were comparable to those (27%) observed in 169 infants with EOGBS during the same period.<sup>74</sup>

The two aforementioned case-control studies<sup>65,72</sup> have accurately defined the risk of LOGBS in infants born to mothers with GBS colonization at VR sites. Pintye et al<sup>67</sup> observed that 25 (33%) of 77 mothers showed GBS colonization during prenatal screening, and the risk of LOGBS was approximately 2-fold higher among neonates who were born to mothers with GBS-positive prenatal screening (crude OR 2.06, CI 1.18–3.609). Lin et al reported that 38% (46 of 122) of mothers of neonates with LOGBS showed GBS colonization at VR sites during prenatal screening. The risk of LOGBS in infants of mothers who showed GBS-positive results on screening was increased (OR 4.15, 95% CI 1.27–13.60).<sup>65</sup> Multivariate analysis performed in a case-control study from South Africa that enrolled 46 infants showed that LOGBS was associated with maternal GBS colonization (OR 2.44, CI 0.88–6.79,  $p=0.088$ ) and GBS bacteriuria (OR 3.49, CI 1.17–10.40  $p=0.025$ ), which serves as a marker for significant maternal colonization. However, approximately 40% of infants diagnosed with LOGBS in that study were exposed to HIV.<sup>75</sup>

Maternal GBS carriage may vary over time,<sup>76</sup> therefore, prenatal GBS colonization may not accurately predict maternal GBS status in the postpartum period. An Italian prospective area-based study that enrolled 100 infants with LOGBS between 2003 and 2010<sup>27</sup> observed that 18 (27%) of 67 mothers showed positive results on testing for GBS at VR sites during prenatal screening (prevalence of GBS carriage at VR sites in the same area was approximately 18%).<sup>77</sup> However, rates of GBS positivity were higher in women in whom GBS carriage was evaluated at the time of LOGBS diagnosis. Approximately 66% of mothers showed positive results during prenatal screening and/or at the time the newborn was diagnosed with LOGBS. Many of these women had received IAP; therefore, postnatal transmission may be implicated in some cases.<sup>27</sup>

## Young Maternal Age

Infants of teenage mothers (<20 years) are predisposed to LOGBS. Multivariate analysis performed in a study by Schuchat et al<sup>64</sup> indicated that maternal age <20 years was independently associated with LOGBS. Teenagers had an approximately 3-fold higher risk of an infant with LOGBS (RR 2.96, CI 1.16–7.51). A case-control study reported an increased risk of LOGBS in neonates born to mothers aged <20 years (adjusted OR 2.32 [1.36–3.98],  $p=0.002$ ).<sup>72</sup> Although young maternal age was more strongly associated with LOGBS among infants born

before the implementation of universal GBS screening, this difference was not statistically significant.<sup>11,20,63,72,78</sup> The underlying mechanism that contributes to the association between young maternal age and LOGBS is unknown; however, young mothers tend to have higher GBS carriage at VR sites and also a weaker immune response or a higher incidence of co-infections, which favor GBS transmission.<sup>11,20,63,78</sup>

## Exposure to the Human Immunodeficiency Virus

A few studies suggest a higher risk of LOGBS in newborns with HIV exposure or infection, despite the similar prevalence of colonization observed in such cases. A cohort study from Belgium reported seven episodes of neonatal GBS infections (LOGBS,  $n=6$ ) among HIV-exposed uninfected neonates. The incidence of GBS infection was significantly higher in infants born to HIV-uninfected mothers.<sup>79</sup> A hospital-based surveillance study performed in Soweto (South Africa, 2004–2008) showed a higher incidence of invasive GBS disease in HIV-exposed than HIV-unexposed infants (4.46 cases/1000 live births [95% CI 3.85–5.13] vs 1.98 cases/1000 live births [95% CI 1.71–2.28]). The higher incidence was most evident in infants with LOGBS (2.36 vs 0.74 cases/1000 live births, RR 3.18, 95% CI 2.34–4.36).<sup>80</sup> A case-control study in South Africa (2012–2014) of 122 neonates with invasive GBS disease (of which 56 were diagnosed with LOGBS) reported that the incidence of EOGBS was similar between HIV-exposed and unexposed neonates (1.1 vs 1.5%,  $p=0.5$ ). However, the risk of LOGBS was 4.7-fold higher in HIV-exposed than in HIV-unexposed infants (2.3 vs 0.5%,  $p<0.001$ ). Although not explicitly stated, the study appears to have been prospectively designed.<sup>75</sup>

## Breastfeeding

The literature that describes breast milk-associated cases of LOGBS is based nearly exclusively on findings of case reports or small case series.<sup>24,37,81–86</sup> Some investigators are of the opinion that breastfeeding may contribute to recurrent episodes of GBS transmission to the newborn,<sup>24</sup> which promotes gut translocation and GBS invasion of the bloodstream. Breast milk with GBS contamination is sometimes associated with symptomatic maternal mastitis,<sup>24</sup> but more often with silent mastitis,<sup>25</sup> with GBS counts sometimes high.<sup>24–27</sup> However, some study reports cases of

LOGBS with GBS confirmed by polymerase chain reaction assays on breast milk despite a sterile culture.<sup>83</sup> Often GBS contaminated breast milk leads to heavy neonatal colonization,<sup>25</sup> and oral administration of GBS is shown to cause systemic infection in animal studies.<sup>22</sup> A recent comprehensive review that summarizes data from 48 cases has shown that breast milk-associated LOGBS has a high recurrence rate and that LOGBS may occur even without RFs other than contaminated breast milk; however,<sup>24</sup> the mechanism underlying breast milk contamination with GBS is unclear. The “retrograde theory” assumes that neonatal colonization occurs at birth and colonization of the oral mucosa contaminates the maternal mammary ducts, owing to the negative pressure created during the sucking action of the newborn. Multiplication of GBS within the mammary ducts increases the bacterial load in milk and re-exposes the neonate to infection during breastfeeding, which results in persistent exposure/colonization of both the neonate and the mother.<sup>37,82,84,86</sup> Alternatively, GBS might be transmitted to the mammary glands following translocation from the gastrointestinal tract through the lymphatics.<sup>87</sup> This additional mode of transmission may explain GBS in the breast milk in women who have never breastfed their newborn but show positive results for VR site colonization.<sup>70</sup>

However, the only case-control study published to date failed to retrospectively confirm an association between breastfeeding and LOGBS.<sup>72</sup> Approximately 0.8–3.5% of women contain GBS in breast milk;<sup>88,89</sup> most breastfed infants do not develop LOGBS. Breast milk has immunomodulating and antimicrobial components (natural secretory immunoglobulin (sIg)A and GBS-specific IgG)<sup>26,90</sup> and plays a key role in protection of infants against infections. A deficiency of these protective agents in breast milk, rather than breastfeeding per se, may increase the risk of LOGBS.<sup>26,91</sup> Le Doare et al<sup>26</sup> prospectively investigated 750 Gambian mother-infant pairs who were followed-up until day 89 of life and observed that sIgA capsular antibodies in colostrum and key immunomodulatory cytokines (tumor necrosis factor- $\alpha$ , interleukin [IL]-6, IL-10, and transforming growth factor- $\beta$ ) were associated with infant serotype III and V GBS colonization, acquisition, and clearance up to 3 months of life. A recent South African study by Dangor et al<sup>91</sup> which included 31 cases of LOGBS reported that breast milk sIgA serotype III antibody concentrations  $\geq 2.52$   $\mu\text{g/mL}$  reduced the risk of LOGBS in infants by 90%.

## Twins

Limited reports in the available literature describe the association between LOGBS and twins. Most studies are case reports or case series, and definitive conclusions cannot be drawn from their findings. Twin pregnancies are associated with higher preterm delivery rates, and prematurity is an important RF for LOGBS. Therefore, it is reasonable to conclude that theoretically, twin pregnancies may be associated with an increased risk of LOGBS. Moreover, twins are exposed to the same maternal genital bacteria, breast milk, and shared nursing care and hospital environments and share genetic susceptibility to infections. A retrospective cohort study performed by Bizzarro et al<sup>92</sup> compared the sepsis concordance rates between 170 monozygotic and 665 dizygotic twin pairs, and the authors observed a significant genetic susceptibility to late-onset sepsis from all pathogens (independent of additional known RFs, such as gestational age or birth weight). In fact, 49.0% ( $p=0.002$ ) of the variance in susceptibility to late-onset sepsis was attributable exclusively to genetic factors and 51.0% ( $p=0.001$ ) to residual environmental factors.

Edwards et al investigated six sets of twins in whom at least one infant had LOGBS disease.<sup>93</sup> A recent review that investigated the association between twin pregnancies and the risk of LOGBS summarizes 13 articles published between 1976 and 2017.<sup>90</sup> The authors observed that among 17 siblings or triplets, most (9 of 17) were born preterm and all but one infant showed serotype III GBS infection on GBS serotyping. LOGBS showed variable delay in presentation in each twin (between 0 hours and 52 days).<sup>93,94</sup> However, these articles did not discuss comparisons with singleton pregnancies.

## Conclusion

Significant gaps exist in the knowledge of LOGBS; limited studies have discussed the RFs for LOGBS, although this information would be useful to implement prevention strategies against LOGBS. Most reports in the literature are retrospectively designed case-control studies, which precludes accurate data collection, and it is not possible to conclusively establish the contributory role of variables such as positive breast milk contamination and maternal GBS colonization at the time of diagnosis of LOGBS, owing to the retrospective design. Well-designed case-control studies are warranted to accurately determine the role of RFs. The best design for such research would be

a large scale, prospective nested case-control study with detailed information available at the time of LOGBS diagnosis in patients and age-matched controls. The knowledge of risk factors and mechanisms underlying LOGBS will contribute to its prevention. Maternal vaccination is likely to be the best preventive strategy of the future.

## Acknowledgments

We are grateful to dr. Monica Imperi (Istituto Superiore di Sanità) who revised the initial draft of the manuscript and gave very valuable suggestions.

## Funding

This research received no external funding.

## Disclosure

The authors declare no conflict of interest.

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