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Original article

**Epidemiology of group B streptococcal disease in infants younger than 1 year in Japan; a nationwide surveillance study 2016-2020**

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**Abstract**

We aimed to define the burden and clinical features of invasive group B *streptococcus* (GBS) disease in infants younger than 1 year in Japan, to explore transmission route of late-onset disease (LOD), and to identify risk factors associated with recurrent GBS disease. We conducted a retrospective, questionnaire-based nationwide surveillance study between 2016 and 2020. A total of 875 GBS cases were identified, including 186 early-onset disease, 628 LOD, and 61 ultra-late-onset disease. Case fatality rate in each age category was 6.5%, 3.0%, and 3.3%, respectively. Patients with meningitis had neurodevelopmental sequelae in 21.5% (64/297). Annual incidence in infants younger than 1 year and in LOD significantly increased from 0.28 to 0.44/1000 livebirths (*p* = 0.021) and from 0.19 to 0.29/1000 livebirths (*p* = 0.046), respectively. Maternal colonization status at the LOD diagnosis was available for 148 mothers, of whom 21/58 (36.2%) had positive rectovaginal swabs and 42/117 (36.2%) had GBS in breastmilk culture. These two sites are potentially infectious routs in LOD. The four leading disease-causing serotypes III, Ia, Ib, and V represented 95% of the available serotypes. Thirty-one recurrent cases were identified, accounting for 3.7% of total patients. A multivariate regression analysis showed that prematurity (*p* = 0.029) and antepartum maternal GBS colonization (*p* = 0.032) were significantly associated with risk for the recurrence. Our findings indicated that GBS disease burden still remains with considerable mortality and morbidity in Japan, and provided important information for developing better strategies for the prevention of GBS disease, including maternal vaccination.

**Keywords**: Group B *streptococcus*; Infant; Incidence; Recurrence; Serotype; Vaccine

**Introduction**

Group B *streptococcus* (GBS, *Streptococcus agalactiae*) colonizes the gastrointestinal and genital tract of around 20% of pregnant women, and can cause invasive GBS disease in neonates and young infants [1-3]. Invasive GBS disease in infants includes sepsis, pneumonia, meningitis, bacteremia, or focal infections, resulting in significant mortality and morbidity [1-4]. GBS infections, according to age at disease onset, are further divided into early-onset (EOD; birth to 6 days), late-onset (LOD; 7 to 89 days), and ultra-late-onset disease (ULOD; older than 90 days of age) [1-3]. The main risk of EOD is vertical transmission from a mother who is colonized with GBS in the anorectum and vagina during pregnancy. The pathogenesis of LOD and ULOD is less well understood than that of EOD, and in some infants the source of infection is unclear [1-5]. Intrapartum antibiotic prophylaxis (IAP) given to the colonized mothers for the reduction of EOD has been adopted in many countries including Japan, but this approach does not prevent LOD or ULOD [3].

The epidemiology of GBS diseases varies considerably geographically and over time. GBS infections remain a burden worldwide, and EOD and LOD incidence were globally estimated at 0.41 and 0.26 per 1000 livebirths, respectively, with estimated case fatality rate (CFR) of 8.4% in 2017 [6]. Systematic reviews noted the paucity of data on GBS from Asia [1,6], highlighting the need for large-scale studies in this region [7,8]. In Japan, we previously performed a national surveillance of GBS diseases in 2003-2010 and 2011-2015 [9,10]. These studies showed that incidence of both EOD and LOD remained stable with 0.08-0.09 and 0.10-0.12/1000 livebirths, respectively, while CFR was improved from 13.6% to 4.5% in EOD and from 8.0% to 4.4% in LOD [9,10].

National guidelines to prevent vertical GBS transmission in Japan were first issued in 2008 and revised in 2011, 2014, 2017, and 2020. The 2017 and 2020 guidelines recommend culture-based universal screening at 35-37 weeks of gestation [11]. IAP is indicated for i) women with a previous infant with invasive GBS disease, ii) women with positive GBS swab culture, except for those who undergo an elective cesarean section, iii) women with an unknown GBS status at delivery with obstetric risk factors (preterm birth, intrapartum fever, or prolonged rupture of membrane >18 hours), and iv) women with GBS bacteriuria during any period of pregnancy [11]. However, implementation of IAP strategies did not show a sufficient effect on the decline of EOD in Japan in our studies to date [9,10].

Vaccines against GBS that can reduce incidence of both EOD and LOD have been tested in clinical trials in pregnant women [12, 13]. Understanding the burden and serotype distribution among infants with GBS disease is crucial in assessing the success of current guidelines as well as the potential impact of a GBS vaccination program in pregnancy. We conducted a retrospective nationwide surveillance study on the updated epidemiology of invasive GBS disease in infants younger than 1 year between 2016 and 2020 in Japan. We further analyzed maternal swab and breastmilk culture status at the time of diagnosis of LOD to determine potential transmission routes, identified potential gaps in implementation of existing IAP guidelines among EOD cases, and delineated clinical features and risk factors associated with recurrence.

**Materials and methods**

**Study design and settings**

A retrospective questionnaire surveillance study was conducted from January 1, 2016 to December 31, 2020. We mailed or emailed structured survey forms to 490 hospitals where educational programs authorized by the Japan Pediatric Society have been adopted for clinical training of pediatrician trainees. Information on invasive cases and their mothers was obtained from chart review at each hospital.

**Clinical data collection**

Structured forms adapted from the previous surveillance were designed in two parts [9,10]. The first sheet contained questions about the number of livebirths, intrauterine transfers, and neonatal (ex-utero) transfers. The second sheet included information on: mode of delivery, evidence of GBS colonization during pregnancy, treatment with IAP, multiple pregnancies, date of birth, birthweight, gestational week at delivery, infant sex, age at onset, initial symptoms, isolation site of GBS (blood, cerebrospinal fluid [CSF], other), clinical syndrome, outcome (alive, died), sequelae at the time of questionnaire (neurodevelopmental, arthropathies), GBS disease recurrence, and serotype of the isolated strain. When cases had multiple infectious episodes, additional data on duration of antibiotic treatment and GBS rectovaginal swab and breast milk culture during each episode were collected. New questions on maternal GBS cultures in breast milk and/or rectovaginal region at the diagnosis of LOD were added to this surveillance.

**Case definitions**

Invasive disease was defined as GBS isolated from a normally sterile site with clinical evidence of invasive infection. Meningitis was defined as a case with a clinical picture consistent with meningitis, and either a positive bacterial culture in the cerebrospinal fluid (CSF) (also including concurrent positive blood culture), or a positive blood culture and CSF pleocytosis. Cases presenting with unstable conditions such as coma and seizure that precluded CSF examination and who had positive GBS blood culture and were later identified with empyema or brain atrophy, were assigned as meningitis. Clinical diagnosis of bacteremia included bacteremia without focus and bacteremic pneumonia. Urinary tract infection and focal infections were included only if accompanied by bacteremia. Arthritis was included when GBS was isolated from joint fluid irrespective of the results of blood culture. Recurrent disease was defined as a new episode of clinical illness in an infant associated with the isolation of GBS from a sterile site occurring after the completion of the therapy for the previous occurrence. Cases were categorized as EOD (0-6 days old), LOD (7-89 days old), and ULOD (90-364 days old), term (≥37 weeks) or preterm (<37 weeks), and low birthweight (<2500 g).

**Estimation of annual incidence**

To estimate the institution-based incidence, we identified the number of EOD, LOD, and ULOD infants born to mothers who were obstetrically managed throughout pregnancy at the relevant hospital (inborn cases). From the case counts, we excluded GBS cases whose mothers were transferred from other hospitals within approximately 2 weeks before delivery (intrauterine transfers) and GBS cases born outside and transferred after the onset of the disease (ex-utero transfers). In Japan, approximately half of newborns are born in private clinics without neonatologists, and infants who are born there and develop invasive GBS disease are transferred to regional hospitals. We used the number of hospital-born livebirths as a denominator of the incidence rate, excluding the number of livebirths after intrauterine transfer and those of ex-utero transfer. Thus, we calculated incidence rate as (**Incidence rate = inborn GBS case count /livebirth total number – livebirth intrauterine transfer – livebirth ex-utero transfer**). This is a method same used in previous studies [9,10].

We also estimated the annual incidence by collecting the number of blood and/or CSF samples positive for GBS in cases from infants under 1 year of age from 1624 facilities that continuously participated in the Japan Nosocomial Infections Surveillance (JANIS) Clinical Laboratory Division throughout the 5-year study. JANIS is a national surveillance program organized by the Ministry of Health, Labour and Welfare of Japan designed to provide representative nation-level epidemiological data on nosocomial infections and antimicrobial-resistant bacteria. JANIS Clinical Laboratory Division captures almost all GBS isolates in Japan, but it does not include clinical information such as prognosis, age in days at onset, clinical diagnosis, or perinatal backgrounds. We calculated the incidence rate of GBS disease using the number of JANIS samples for positive GBS as the numerator and the number of total livebirths from the Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/toukei) as the denominator. Anonymized data was check for multiple notifications through case review identified by date of birth and birthweight.

**Statistics**

Fisher’s exact test was used to compare distributions of categorical variables. Mann–Whitney U test was used to compare continuous variables. Linear trends in incidence rates were evaluated using the Cochran-Armitage test. To determine risks associated with recurrence, we used a logistic regression model. Because birthweight and gestational age at birth are closely correlated, only gestational age was used as an explanatory factor in a multivariate regression analysis. A two-tailed significance level of *p* <0.05 was used. SSPS for Windows (version 26.0, SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.

**Ethical aspects**

The study was approved by the Ethics Committee of Kobe City Nishi-Kobe Medical Center, Kobe (approval number: 2020-31); review board approval in each institution was not required because of the assessment of anonymized surveillance. The anonymous data stored in the JANIS database were exported and analyzed following approval by the Ministry of Health, Labor and Welfare (approval number: 0623-9) according to Article 32 of the Statistics Act.

**Results**

Of the 490 institutes where questionnaires were sent, 343 were recovered (70.0 % response rate) including at least two institutes in all 47 prefectures of Japan. Of the 343 institutes, 201 have a neonatal intensive care unit (NICU), and the remaining 142 are regional centers without an NICU; 241 institutes reported 1-20 cases, and 102 institutions had no cases. Total livebirths in the 343 institutes were 865 984 including 48725 neonates delivered after maternal transfer. During the 5-year period, we identified 875 cases of GBS in infants younger than 1 year, comprising of 186 EOD, 628 LOD, and 61 ULOD. Multiple infectious episodes were identified in 31 cases (two times in 30 cases, three times in one case); hence the total patient number was 843.

**Demographic features and CFR in EOD, LOD, and ULOD**

We showed demographic features in Table 1 and prognosis according to age groups and clinical diagnosis in Table 2. Most EOD cases (137 [73.7%]) occurred within 48 hours of birth, and 40 (21.5%) and 48 (25.8%) were in preterm infants and in low birthweight infants, respectively. The overall EOD CFR was 6.5% (12/186), significantly higher in preterm infants than that in full-term infants (8/40 [20.0%] vs 4/146 [2.7%], *p* < 0.001, odds ratio [OR]; 8.9 [95% CI, 2.5-31.3]). CFR in early preterm (22-33 weeks’ gestation) infants (22.6%, 7/31) was double that in late preterm (34-36 weeks’ gestation) infants (11.1%, 1/9). 69.7% (115 EOD cases in 165 examined) had negative GBS swab cultures during pregnancy.

 The median (interquartile range [IQR]) patient age at the diagnosis for LOD was 27 (17-45) days, and 158 (25.2%) and 186 cases (29.6%) were in preterm and low birthweight infants, respectively. Two major clinical diagnoses included bacteremia (358 [57.0%]) and meningitis (229 [36.5%]). Rare manifestations such as parotitis with bacteremia (2), infective endocarditis with bacteremia and cerebral infarction, purulent myositis with bacteremia, and deep abscess (each 1) were identified. The overall LOD CFR was 3.0% (19/628). Like in EOD, CFR in preterm LOD infants was significantly higher than that in full-term infants (10/155 [6.5%] vs 9/471 [1.9%], *p* = 0.012, odds ratio [OR]; 3.5 [95% CI, 1.4-8.9]). CFR in early preterm infants (7.1%, 8/112) was higher than that in late preterm infants (4.3%, 2/46).

 ULOD was identified in 61 cases. Three quarters (46 [75.4%]) developed disease at 3 and 4 months of age with male predominance (40 [65.6%]). Two significant characteristics in ULOD cases were identified distinctive from those in EOD and LOD cases; preterm birth (65.6% vs 21.2% and 29.4%, respectively) and infants with underlying conditions other than prematurity (Table 1) (13.1% vs 1.6% and 2.6%, respectively).

**Sequelae**

The rate of neurodevelopmental or arthropathy sequelae in EOD, LOD, and ULOD was 16.1%, 9.7%, and 11.5%, respectively (Table 2). Details were shown in Table S1. Infants with meningitis had the highest rate of neurodevelopmental sequelae at 20-28% in each age category and at 21.5% (64/297) of total cases. The sequelae in individuals with meningitis were more prominent in preterm infants; 60% in EOD, 26% in LOD, and 50% in ULOD.

**Annual incidence and trend over time**

From 2016 to 2020, annual incidence of infants younger than 1 year with invasive GBS diseases was 0.28, 0.34, 0.24, 0.35, 0.45/1000 livebirths in each year, respectively, giving an average annual incidence rate of 0.33 (95% CI 0.30–0.35) per 1000 livebirths (Fig. 1a). The increased trend during the 5-year study period was significant (*p* = 0.021). We also estimated the incidence through JANIS databases and national birth data. The number of infants aged <1 year whose blood and/or CSF cultures positive for GBS was identified as 280, 276, 310, 277, and 334 in 2016, 2017, 2018, 2019, and 2020, respectively. Using national data on livebirths (976 979, 946 065, 918 397, 865 234, and 840 832 in each study year, respectively) as the denominator, the average incidence rate during the 5-year study period was 0.32 (95% CI 0.30-0.36) per 1000 livebirths with a significant increasing trend (*p* < 0.001). These incidences and the trend were quite similar to our results (Fig. 1b).

When stratified by age group, the incidence of EOD (average; 0.09, [95% CI 0.07-0.10]/1000 livebirths) and ULOD (average; 0.03 [95% CI 0.02-0.04]/1000 livebirths) remained stable, while the incidence of LOD significantly increased from 0.19/1000 livebirths in 2016 to 0.29/1000 livebirths in 2020 (*p* = 0.046) (Fig. 1a). Overall incidence of LOD during a 5-year study period was 0.21 (95% CI 0.19-0.24)/1000 livebirths. Among subclasses of LOD clinical diagnosis, there was no significant change in trend.

**Serotype distribution**

Among sites that collected isolates, serotype data were available for 86 of 186 cases of EOD (46.2%), 161 of 628 cases of LOD (25.6%), and 17 of 61 cases in ULOD (27.9%) (Fig. 2). Among a total 264 cases with EOD, LOD and ULOD, serotypes III (149, 56.4%), Ia (59, 22.3%), Ib (31, 11.7%), and V (13, 4.9%) predominated and were responsible for 95% of pathogens determined. Serotype distribution did not significantly differ in each study year and when stratified in EOD, LOD, and ULOD. In infants with meningitis, serotype III was predominant with 13 of 20 EOD cases (65.0%) and 47 of 71 LOD cases (66.2%).

**Maternal GBS status at the diagnosis of LOD**

To determine possible transmission routes in LOD, we collected data on maternal colonization status at the diagnosis of LOD. Of 628 LOD cases, maternal colonization status at the diagnosis of LOD was available for 148 mothers, of whom 21/58 (36.2%) had positive rectovaginal swabs and 42/117 (35.9%) had GBS in breastmilk culture. In three mothers, both rectovaginal swab and breastmilk culture grew GBS at the time of LOD (Table S2). The positive predictive value of having a GBS positive rectovaginal culture at time of LOD if antenatal rectovaginal colonization was positive was 47.6% (10/21) and the negative predictive value was 67.6% (25/37). Of women who had GBS in breastmilk culture at time of LOD, 11/42 had GBS positive antenatal rectovaginal colonization. Either breast milk culture, rectovaginal swabs or both were positive in 60 mothers of 148 investigated (40.5%).

**Recurrent cases**

Recurrent infectious episodes were identified in 31 infants, accounting for 3.7% of all patients; 30 infants had two episodes and 1 infant had three episodes (Table 3). Sixteen (51.6%) infants were preterm. Of the 21 cases whose maternal antenatal GBS screening test was known, 12 (57.1%) had a positive result at antenatal screening. Two infants died during the second episode. Median age at the onset of the first and second episodes was 15 (range: 0-81) days and 44 (24-119) days, respectively. The median interval from completion of initial therapy to onset of second episode was 9 (3-98) days, which was significantly shorter (7 vs 26 days, *p* = 0.004) in cases if the first episode was LOD than in cases where the first episode was EOD. Breast milk samples from four (40%) of 10 at the first episode and eight (50%) of 16 in the second episode had a positive GBS culture result. In four of 7 cases, where data were reported, breastfeeding was stopped after the first or second episode. In 13 cases, isolates were serotyped in both the first and second episodes, and were all consistent in both episodes. Serotype III was predominant in 10 of 13 cases.

 A univariate analysis showed that birthweight, gestational age, and maternal antenatal colonization were associated with increased risk of GBS recurrence (Table S3 and Table 4). When the categorical predictor variables were modelled together in a multivariate logistic regression model, the association of GBS recurrence with prematurity (OR 0.92 [0.85-0.99] [every 1-week increase in gestational age], *p* = 0.029) and maternal antenatal colonization (OR 2.72 [95% CI 1.09-6.75], *p* = 0.032) remained significant (Table 4).

**Twin cases**

Three pairs of twins were affected with invasive GBS diseases (Table 5). Two pairs were associated with premature birth, and one twin of one pair developed recurrent infections. Seven episodes all occurred as LOD, presenting with bacteremia (*n* =5) and meningitis (*n* =2). Three pairs of twins had intervals of GBS disease onset of 1, 2, and 25 days. All six infants survived without sequelae.

**Discussion**

Our study defines the burden of invasive GBS disease in infants younger than 1 year in Japan through a nationwide surveillance. We have continued to conduct the surveillance every 5-7 years using the same methods since 2003 [9,10], and therefore provide comparable information on changes in the prognosis and incidence for Japan. Compared with the previous study [10], this study had an enhanced response rate from 50% to 70%, and a higher number of institutes participating, indicating increased recognition of the importance of GBS disease in Japan over time. The total 875 infectious episodes are the largest subjects among the Asian GBS studies in childhood ever reported [6]. Furthermore, our estimates of the annual incidence through the hospital-based approach were quite similar to those through population-based JANIS data and national birth cohort, supporting the validity of our results. Based on the comparison between numbers of JANIS enrollment and our collection, approximately 60% of national GBS disease cases younger than 1 year would be captured in this study.

We found a significant increase in the incidence of infants with GBS disease younger than 1 year between 2016 and 2020 (0.33 [95% CI 0.30–0.35] per 1000 livebirths) and compared to our 2011-2015 study (0.22 [95% CI 0.19-0.26] per 1000 livebirths) [10]. This increase was mainly driven by an increase in LOD (overall incidence: 0.21 [95% CI 0.19-0.24] per 1000 livebirths), which was 1.8 times higher than the 2011-2015 study (overall incidence: 0.12 [95% CI 0.11–0.14] per 1000 livebirths) [10]. A JANIS data-based study showed that case count of GBS disease aged younger than 1 year was significantly increased between 2010 and 2016 [14]. Moreover, we first showed such significant increase as the incidence in a more recent study period. The emergence of more virulent GBS strains such as serotype III clonal complex 17 might be an explanation of this increase [15], but our study showed that serotype distribution did not significantly differ throughout a 5-year study period (data not shown). Furthermore, annual rate of prematurity, another risk factor for LOD [15], changed little among LOD cases in the current study. Thus, the exact reasons of the increase trend were unclear. A similarly increased trend in LOD was shown from two Australian tertiary facilities between 2000 and 2014 [16]. In the United States, from 2006 to 2015 overall LOD incidence remained stable, while LOD incidence due to serotype III increased significantly from 0.12 to 0.20 per 1000 livebirths [17]. On the other hand, a population-based study in England showed no significant trend over 20 years (1998-2017) in infants aged <90 days [18]. A 2009-2010 study in Germany showed that EOD incidence was 32% lower compared to a 2001-2003 study, while LOD incidence remained stable [19]. The considerable discrepancies in incidence trends among these studies and ours might be explained by differences in the study period, true geographic variations, or the timing and prevention strategies against vertical transmission [20].

Despite the introduction of universal screening strategies to prevent EOD from 2008, the incidence in Japan has remained unchanged at 0.08-0.09/1000 livebirths, including our current study [9,10]. The reasons that EOD cases have not reduced remains unclear. One of the potential explanations is that EOD had declined prior to the first issue of Japanese guidelines because more than 40% of institutes had adopted the universal screening strategies before 2008 [9]. However, the more plausible explanation is attributed to a low rate of adherence of guidelines. A nationwide surveillance of maternal screening methods showed cultures before 35 weeks’ gestation of 23%, culture site at vagina alone of 60%, and no use of enrichment medium in cultures of 66% [21]. Based on a surveillance study of private clinics, only 48% of midwives performed antenatal GBS screening test, and 54% administered antibiotic prophylaxis to GBS-positive women in labor [22]. These findings would reflect the high negative rate of 69.7% for antenatal cultures among EOD cases in this study, and conversely can be interpreted as room left for further reduction if guidelines were better implemented.

To explore the potential infectious routes of GBS transmission, we collected data on the maternal colonization status at the diagnosis of LOD. Of 148 LOD cases where maternal GBS status was available, breast milk and/or rectovaginal cultures were positive in 40.5%, higher than the positivity rate at antenatal screening of these mothers of 31%. At the same time over 85% of these mothers received IAP, leaving a conundrum about relationship between maternal colonization at delivery and LOD. We previously reported similar findings in a longitudinal study during the postpartum period [23], which showed delayed GBS colonization in infants born to GBS-colonized mothers who receive IAP. A recent French prospective study [5] also showed that in 890 mother-baby pairs with 2 months of follow-up, the infant GBS colonization rate was 7% at birth, 21% at 3 weeks, and 24% at 2 months of life. These findings suggested that delayed GBS colonization might stem from two modes of GBS acquisition: a vertical transmission that is lowered but not suppressed by IAP and a horizontal transmission after delivery that likely occurs through nursing and possibly breastfeeding [5]. Collectively, antepartum and postpartum maternal colonization in the vagina and/or breast milk are important potential sources for the development of LOD.

We identified 31 cases with recurrent episodes, accounting for 3.7% of the total 843 infants. To our knowledge, this is the largest case series with recurrence ever reported [3]. Notably, maternal colonization of 57.1% in the recurrent cases was much higher than for EOD (30.2%) and LOD (31.2%) infants, suggesting that further investigation of mode of GBS transmission in recurrence is warranted. We showed that prematurity and positive maternal antenatal colonization are risk factors for recurrence. The former factor is consistent with findings in a recent large cohort in UK, Ireland, Germany and Switzerland [24]. Premature infants are characterized by disturbances of microbiome development due to frequent use of antibiotics and reduced contact with the maternal microbiome [24, 25].Taken together, premature infants with maternal and subsequent neonatal GBS colonization may be at higher risk for invasive GBS disease recurrence.

 Our study has potential limitations. First, this was a retrospective study through a questionnaire survey. However, response rates and the number of participating institutions substantially increased from the previous two studies [9,10]. Comparing our data to JANIS, we captured approximately 60% of cases nationwide, enhancing the accuracy and validity of our study. Second, data collection of serotypes was subject to information bias due to missing data. However, there is no significant difference in clinical backgrounds between tested and untested patients, minimizing this bias. Despite this limitation, findings that four leading serotypes Ia, Ib, III, and V are responsible for 95% of total cases and are components of the multivalent vaccine currently under development [12, 13] are very important to consider for the introduction of maternal vaccination. Third, we have described details of the sequelae, the incidence of which was higher in those who developed meningitis at 20-28% in each age category. However, this percentage might be underestimated because we collected such sequelae principally at the time of questionnaire without severity. Neurological impairments, especially in mild form or intellectual deficits might be later recognized during long-term follow-up [26, 27].

In conclusion, we showed a significantly increased trend in LOD GBS disease and gaps in prevention strategies in Japan. The finding that maternal colonization in the vagina and/or in breast milk is associated with LOD will help inform policy for investigation in LOD case to improve the evidence base for this, as well as considering premature infants at risk of recurrent disease. Given that considerable mortality and sequelae still remain in Japan, maternal vaccination is likely to be the best preventive strategy.

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**Contributors**: Meiwa Shibata and Kousaku Matsubara conceptualized and designed the study, and had full access to all the data. Data collection and analysis were performed by all authors. The first draft of the manuscript was written by Meiwa Shibata, Kousaku Matsubara and Kirsty Le Doare. All authors critically reviewed the manuscript and approved the final manuscript as submitted.

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**Legends to figures**

**Fig. 1**

Average annual incidence of invasive GBS disease in infants younger than 1 year between 2016 and 2020.

**a** Incidence of each age category; all infants younger than 1 year (blue line), early-onset disease (EOD) (gray line), late-onset disease (LOD) (orange line), and ultra-late-inset disease (ULOD) (yellow line). **b** Incidence in infants with invasive GBS disease younger than 1 year from data in the current study (blue line) and those in the Japan Nosocomial Infections Surveillance (JANIS) (orange line). Vertical bars represent range of 95% CI.

**Fig. 2**

Serotype distribution in early-onset disease (EOD) (*n* = 86), late-onset disease (LOD) (*n* = 161), and ultra-late-onset disease (ULOD) (*n* = 17). Number in figures denotes case number of each serotype.