

Comparison of pre- and intrapartum screening of group B streptococci and adherence to screening guidelines: a cohort study

Mirjam Kunze¹ · Katharina Zumstein² · Filiz Markfeld-Erol¹ · Roland Elling^{2,3} · Fabian Lander^{2,4} · Heinrich Prömpeler¹ · Reinhard Berner^{2,4} · Markus Hufnagel²

Received: 13 December 2014 / Revised: 12 April 2015 / Accepted: 14 April 2015 / Published online: 30 April 2015
© Springer-Verlag Berlin Heidelberg 2015

Abstract Implementation of guidelines for group B streptococcal (GBS) prepartum screening (PS) rarely has been prospectively evaluated. To assess PS at 35–37 weeks of gestation and compare its predictive value to that of an intrapartum screening (IS) within 7 days of delivery, a surveillance cohort study was conducted at a tertiary care center in Freiburg, Germany, during 2011–2012. Study participants included 937 pregnant women who had intrapartum cultures taken for vaginal and rectal GBS colonization. Colonization status was compared to PS, and intrapartum antibiotic prophylaxis (IAP) rates calculated. The neonates were tested for GBS transmission via cultures from their throats and external ear canals. While 67.5 % (633/937) of study participants had a PS, only 22.7 % (144/633) underwent a fully guideline-compatible PS. However, maternal GBS colonization rates were similar when comparing PS (18.5 % [117/633]) versus IS (17.0 % [133/784]). The positive predictive value of a positive PS result for GBS positivity at delivery was

77.2 %. Women with a positive PS received IAP in 89.3 % of cases (75/84). The capsular serotype distribution pattern of colonizing GBS strains has not changed in comparison to our 2003–2004 study—one with a similar study design.

Conclusions: Improved strategies for adoption of prepartum GBS screening are needed.

What is Known:

- The prediction of prepartum GBS screening for intrapartum colonization status has not been well studied.
- Longitudinal studies of GBS screening are needed for screening program evaluations and vaccine development.

What is New:

- The rate of GBS screening has improved over 10 years, and intrapartum GBS colonization prediction was accurate.
- Serotype distribution was stable and suggests the potential long-term efficacy of GBS vaccines.

Communicated by David Nadal

Revisions received: 10 March 2015 / 12 April 2015

✉ Markus Hufnagel
markus.hufnagel@uniklinik-freiburg.de

Mirjam Kunze
mirjam.kunze@uniklinik-freiburg.de

Katharina Zumstein
akzumstein@gmail.com

Filiz Markfeld-Erol
filiz.markfeld-erol@uniklinik-freiburg.de

Roland Elling
Roland.Elling@umassmed.edu

Fabian Lander
fabian.lander@uniklinikum-dresden.de

Heinrich Prömpeler
heinrich.proempeler@uniklinik-freiburg.de

Reinhard Berner
reinhard.berner@uniklinikum-dresden.de

¹ Department of Gynecology and Obstetrics, University Medical Center Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany

² Section of Pediatric Infectious Diseases and Rheumatology, Center for Pediatrics and Adolescent Medicine, University Medical Center Freiburg, Mathildenstr. 1, 79106 Freiburg, Germany

³ Present address: Division of Infectious Diseases and Immunology, University of Massachusetts Medical School, Worcester, MA, USA

⁴ Present address: University Children's Hospital, Technische Universität Dresden, Dresden, Germany

Keywords Colonization · Group B streptococcus (GBS) · Intrapartum antibiotic prophylaxis (IAP) · Neonatal · Screening · *Streptococcus agalactiae*

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
CDC	Centers for Disease Control and Prevention
EOD	GBS early-onset disease
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GBS	Group B streptococcus
IAP	Intrapartum antibiotic prophylaxis
IS	Intrapartum screening
MIC	Minimum inhibitory concentrations
NPV	Negative predictive value
PPV	Positive predictive value
PS	Prepartum screen
RVS	Recto-vaginal swab

Introduction

Group B streptococcus (GBS), otherwise known as *Streptococcus agalactiae*, is the leading cause of early-onset neonatal sepsis, frequently associated with significant morbidity and mortality [21, 22]. In 1996, the first GBS screening guidelines were implemented by the Centers for Disease Control and Prevention (CDC), together with the American College of Obstetricians and Gynecologists (ACOG) [6]. In 2002, these guidelines were updated and a culture-based screening approach was advised for all pregnant women between 35 and 37 weeks gestation [20]. This same screening strategy continues to be recommended by the CDC and ACOG today. In Germany, at the national level, guidelines issued in 2000 and subsequently revised in 2006, 2008, and 2010 also have been supporting a culture-based screening approach [3]. Currently, GBS screening in Germany is optional and not reimbursed by the German health insurance system. Over the course of the last decade, most countries in Europe have adopted a preventative strategy which includes screening cultures for all pregnant women, as well as intrapartum antibiotic prophylaxis (IAP) for GBS carriers. While this has led to a notable decline in GBS early-onset disease (EOD) [20], it simultaneously has given rise to an increase in antibiotic resistance [18]—a rising public health risk worldwide. Only a few European countries, such as the Netherlands and the UK, favor a risk factor-based approach [18]. Independent of the type of GBS screening conducted, the incidence of GBS

late-onset disease (LOD) in neonates has remained unchanged [25].

In 2003–2004, shortly after introduction of the first national screening guidelines in Germany, we performed a single-center surveillance study to evaluate GBS colonization and transmission rates in pregnant women and their infants. This was conducted at the Freiburg University Medical Center in Freiburg, Germany [14]. Our results showed that maternal colonization occurred in 21.1 %, while transmission from mother to infant took place in 11.2 %. IAP was administered in only 39 % of the GBS-positive cases. We undertook our current study with the aim of documenting the adoption of prepartum GBS screening, assessing IAP rates, and gauging their effects on GBS transmission. In addition, we compared the results of the prepartum screening with intrapartum screening and then further analyzed the effect of intrapartum colonization density in pregnant women upon transmission from mother to infant. Intrapartum screening for this purpose was defined as screening within 7 days prior to delivery, which strictly speaking is not in fact a true intrapartum screening. In order to clearly distinguish this late GBS colonization status—which is most relevant for neonatal GBS transmission—from prepartum colonization, we labeled it intrapartum screening. Finally, capsule type distribution and antibiotic resistance were determined and their trends compared to our study from 2003 to 2004. By performing this comparison, our goal was to monitor factors that influence the adherence to GBS screening guidelines and thereby to identify aspects of the screening process that may be in need of improvement.

Materials and methods

Setting and study design

We conducted the surveillance cohort study from February 2011 to January 2012 at the Freiburg University Medical Center, a tertiary care facility in southwestern Germany. All pregnant women presenting for delivery in the obstetrical department were invited to participate in a prospective GBS intrapartum screening (IS) study. For screening purposes, the recommended sampling technique, a recto-vaginal swab (RVS), was performed [3, 25]. A screen was considered intrapartum when swabs were taken from a pregnant woman who presented to the delivery room and gave birth within 7 days. The result of the IS was then compared to the women's prepartum screening (PS), which was obtained from the local obstetrician performing the prenatal care. The microbiological method used for PS was documented and was not standardized. In the event that no screening culture result was available and the pregnant women presented at the outpatient obstetric clinic of the University Medical Center in Freiburg before

labor had started, PS was conducted according to the standardized protocol.

In Germany, prenatal screening is advised at 35–37 weeks gestation [3]. The study defined prepartum screening as cultures obtained before 38 weeks of gestation. We based the decision for chemoprophylaxis at delivery either upon a positive screening result at week 35–37, or else upon the latest available positive culture prior to delivery. Infants delivered by our pregnant women were cultured for GBS colonization by swabbing both the infant's throat and the external ear canals between day 1 and day 7 of life.

In the event of a positive GBS culture, IAP was administered to the pregnant woman in labor. Standard IAP consisted of 2 g of ampicillin administered intravenously, followed by 1 g given intravenously every 4 h until delivery [3]. The optimal IAP was defined as initiation of antibiotics at least 4 h prior to delivery [25]. If the patient was allergic to penicillins, cefuroxime or clindamycin was administered according to current CDC and national guidelines [3, 25]. Clindamycin only was given when susceptibility results were documented. Healthy-appearing infants born from mothers who had not received chemoprophylaxis at least 4 h ahead of delivery were monitored for ≥ 48 h.

Data from the obstetrical charts were collected, with neonatal data related to GBS infection taken from patients' clinical charts. From all GBS-positive women who participated in the study, clinical data regarding prepartum GBS screening were collected according to a standardized questionnaire. The information was retrieved either from the patient's pregnancy documentation pass record or else by contacting her obstetrician or the obstetrician's laboratory by telephone or fax. The following data were collected: time point of prepartum GBS screening, anatomical location of specimen collection, and detection method used for GBS screening (including the culture medium).

The study protocol was approved by the Institutional Review Board of the University Medical Center, Freiburg, Germany (approval number 10/11). All women who participated provided written, informed consent before their and their infants' involvement in the study. Participation in the prospective part of the study included a retrospective review of the women's prepartum GBS status.

Microbiological methods

Cultures from pregnant women were taken first from the lower vagina, then from the rectum, using the same swab. Cultures from infants were taken first from the throat, then from both external ear canals, using the same swab. Swabs were placed in a transport medium and inoculated both in selective broth media for enrichment (Todd-Hewitt Broth supplemented with 10 $\mu\text{g/ml}$ colistin sulfate and 15 $\mu\text{g/ml}$ nalidixic acid) within 24 h at 37 °C for 20–24 h, as well as

on selective agar (i.e., sheep blood agar containing 10 $\mu\text{g/ml}$ colistin sulfate and 5 $\mu\text{g/ml}$ oxolinic acid) according to the German guideline [3]. In cases where direct plating on selective agar did not reveal bacterial growth but the selective broth did, the broth was sub-cultured on selective agar plates. The density of GBS growth in colonized mothers who underwent intrapartum screening was semi-quantitatively evaluated [2, 26]: 1–50 colonies per 10 μl inoculum was considered low colonization (1+); 51–100 colonies, moderate colonization (2+); and over 100 colonies, high colonization (3+). GBS colonies on plates were confirmed by CAMP test or latex agglutination (Remel Streptex, Remel Europe Ltd., Dartford, England).

For antibiotic susceptibility testing, Mueller Hinton agar supplemented with 5 % defibrinated horse blood and β -NAD (Biomérieux, Marcy l'Etoile, France) was used. The minimum inhibitory concentrations (MICs) of penicillin, cefotaxime, erythromycin, and clindamycin were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, version 2.0 [9]. Inducible clindamycin resistance was detected by D-zone testing.

Serotyping of GBS was performed by slide agglutination with STREP-B-Latex antisera against serotypes Ia, Ib, and II–IX (Serum Statens Institute, Copenhagen, Denmark). The protocol employed was that recommended by the DEVANI consortium [1]. For genotyping of GBS capsular polysaccharides, the multiplex-PCR method from Imperi et al. was used [12].

Statistical analysis

For statistical analysis, Microsoft Excel and GraphPad Prism V.6 were employed. Results were expressed either as a mean \pm SD or as a percentage of the total number of isolates or patients. Differences in proportions were compared using either a chi-square test or Fisher's exact test, as deemed appropriate. All statistical tests were performed two-tailed and considered significant if the *p* value was <0.05 .

Results

A total of 1497 live births were recorded during the study period. In 937 of the pregnant women who agreed to participate in the study, a full data set was obtained. The study participants' characteristics are shown in Table 1. Of the 937 participants, 633 had a prepartum GBS screening. In 502 cases, the PS was performed between 35 and 37 weeks gestation, or within 5 weeks prior to delivery. Although 937 study participants underwent intrapartum GBS screening, only 784 women had the screening within the defined time frame of 7 days prior to delivery. Finally, GBS isolates were retrieved from 695 mother-infant pairs. Meanwhile, 597 mother-infant

Table 1 Study participants' characteristics ($n=937$)

Characteristics	Number	Percentage
Median maternal age (years)	30.8 (15–45)	n.a.
Primipara	509	54.3
Multipara	428	45.7
Singleton gestation	915	97.7
Twins	22	2.3
Mean gestational age at delivery (weeks)	38.8±1.6	n.a.
41–42	89	9.5
37–40	783	83.6
33–36	61	6.5
31–32	1	0.1
<31	2	0.2
Unknown preterm delivery	1	0.1
Type of delivery		
Vaginal	518	55.3
Cesarean delivery	419	44.7
Planned cesarean	181	19.3
Cesarean after start of labor	238	25.4
Preterm rupture of membranes >18 h	87	9.3
Fever sub-partu	5	0.5
GBS bacteriuria	13	1.4
Previous child born with GBS disease	3	0.3

n.a. not applicable

pairs had both a pre- and an intrapartum GBS screening. Among the infants, 23 had a positive GBS surface culture.

Prepartum GBS screening and colonization rates

Of the 937 pregnant women who had an IS, seven were not offered a PS, either because they had experienced a documented case of GBS bacteriuria at some point during their pregnancy or else because they had a history of a previous child with GBS disease. Of the remaining 930 pregnant women, 68.1 % (633/930) received PS. Over three quarters of the screening was done at the gynecologists' private practices, while one quarter was completed in the outpatient obstetric clinic at the Freiburg University Hospital (Table 2). In accordance with national guidelines, screening was performed between 35 and 37 weeks of gestation in 59.3 % (375/633) of the cases (Table 2). While 66.4 % of the women (420/633) had a RVS taken, the remainder received only a vaginal swab. A selective broth medium for enrichment of GBS was used in just 29.2 % of cases (185/633)—primarily in women screened at the hospital—whereas a selective agar medium was employed in 94.9 % of cases (601/633).

Hence, overall, full adherence to national screening guidelines—including timing of screening, type of specimen collection, and processing—was markedly low (i.e., 22.7 % [144/633]), especially when screening was performed by

gynecologists in private practice (i.e., 3.1 % (15/482)). The overall colonization rate of pregnant women was 18.5 % (117/633). Interestingly, however, the colonization rate among women who had had their screening done by gynecologists in private practice fell within the very same range (i.e., 17.8 % [86/482]) as the overall colonization rate, despite the fact that an enrichment broth was only quite rarely used.

Intrapartum GBS screening, density, and colonization rates

In 83.7 % (784/937) of the women who received intrapartum GBS screening, screening was performed within 7 days of delivery. Adherence to recommended screening techniques was nearly absolute: RVS in 99.8 % and use of selective broth media and selective agar plates in 100 % (Table 2). The colonization rate among women participating in the IS was 17.0 % (133/784). GBS density was determined in 85 of 133 GBS-positive women. Over half the women (i.e., 54.1 % [46/85]) showed high (i.e., 3+) colonization, whereas 32.9 % (28/85) had low (i.e., 1+) and 12.9 % (11/85) had moderate colonization (i.e., 2+).

GBS transmission rates

The overall neonatal colonization rate was low (i.e., 3.3 % [23/695]). The GBS transmission rate for women with a positive GBS screening at 35–37 weeks or within 5 weeks prior to delivery was 6.6 % (8/122) (Table 3A), while for GBS-negative women, the rate was 1.9 % (9/475). The corresponding transmission rates in women screened intrapartum were 10.9 % (12/110) and 1.6 % (8/487), respectively (Table 3B). The difference in transmission rates between pre- and intrapartum screening was statistically not different ($p=0.238$, RR 1.664 [0.706–3.919]). Capsular serotype was 100 % concordant between mothers and their infants. Among the cohort, no case of EOD was noted.

Comparison of prepartum to intrapartum screening

A positive prepartum screening (i.e., either in week 35–37 of gestation or else within 5 weeks prior to delivery) had a positive predictive value of 77.2 % for a positive IS within 7 days of delivery (Table 4A). The corresponding figures for a negative predictive value, sensitivity, and specificity were 92.2, 71.0, and 94.3 %, respectively (Table 4A). When prepartum screening was performed in full compliance with German guidelines, these numbers improved (Table 4B). Discordant results from prepartum versus intrapartum screens were associated with a specific serotype. In women who switched from a negative prepartum GBS screen (at 35–37 weeks of gestation) to a positive intrapartum screen (i.e., 6/18), serotype II isolates were more commonly discovered than in concordant

Table 2 Characteristics of the prepartum ($n=633$) versus the intrapartum screening ($n=937$) cohort

	Prepartum screening ($n=633$)		Intrapartum screening ($n=937$)		p (chi-square) (95 % CI)
	Number	Percentage	Number	Percentage	
Screening at practitioner	482	51.8	–	–	n.d.
Screening at university hospital	151	16.1	937	100	n.d.
Time point of screening					
35–37 weeks gestation	375	59.3	61	6.5	n.d.
<35 weeks gestation	211	33.3	4	0.4	n.d.
>37 weeks gestation	47	7.4	872	93.1	n.d.
≤7 days of delivery	–	–	784	83.7	n.d.
>7 days of delivery	–	–	153	16.3	n.d.
Type of screening material					
Recto-vaginal	420	66.4	935	99.8	<0.0001 (0.631–0.705)
Vaginal	211	33.3	2	0.2	<0.0001 (38.93–626.4)
Unknown	2	0.3	–	–	n.d.
Type of screening media					
Selective broth	185	29.2	937	100	<0.0001 (0.259–0.330)
Blood CNA plate	601	94.9	937	100	<0.0001 (0.933–0.967)
GBS antigen test	6	0.9	–	–	n.d.
GBS colonization	117	18.5	133	17.0	n.s. (0.870–1.365)

CNA colistin-nalidixic acid agar, 95 % CI 95 % confidence interval, n.d. not done, n.s. non-significant

screening results (i.e., 3/44; $p=0.007$, RR 4.889 [1.369–17.46]). By contrast, serotype III isolates more commonly were seen in concordant screening results (i.e., 13/44) than in situations where the prepartum status for serotype III was negative but the intrapartum screen positive (i.e., 1/18; $p=0.040$, RR 5.318 [0.749–37.72]). Unfortunately, discordant GBS strains that were positive at PS but negative at IS were not available for serotype testing. In cases of discordant results between prepartum and intrapartum GBS screening, no neonatal GBS transmission occurred.

Table 3 GBS transmission from pregnant mother to infant with respect to prepartum screening at 35–37 or ≤5 weeks prior to delivery (A) versus intrapartum screening within 7 days prior to delivery (B) status

	Neonatal culture		
	GBS positive	GBS negative	Total
A. Prepartum screening (35–37 weeks or ≤5 weeks prior to delivery)			
GBS positive	8	114	122
GBS negative	9	466	475
Total	17	580	597
B. Intrapartum screening (≤7 days of delivery)			
GBS positive	12	98	110
GBS negative	8	479	487
Total	20	577	597

Influence of GBS density shown at intrapartum screening upon transmission

GBS density only was determined at intrapartum screening. We found a significant correlation between GBS density within 7 days of delivery and GBS transmission to the neonate. Women with a 3+ density (>100 colonies per 10 μ l) transmitted GBS in 17.4 % of cases (8/46), whereas no GBS transmission (0/28) was noted in women who had a 1+ density (<50 colonies per 10 μ l; $p=0.0195$). The rate of transmission in 2+ density (50–100 colonies per 10 μ l) was 9.1 % (1/11).

Intrapartum antibiotic prophylaxis

Rates of IAP application were high. Women who screened positive for GBS during weeks 35–37, or within 5 weeks of delivery, received IAP in 89.3 % of cases (75/84). This rate was comparable to women who had had a positive intrapartum screen (i.e., 92.0 % [103/112]; $p=0.521$, RR 0.971 [0.885–1.065]). Only 57.1 % (48/84) of GBS-positive women during PS received IAP at least 4 h or more prior to delivery.

Antibiotic resistance of GBS isolates

No GBS isolate was resistant to penicillin or cefotaxime. Resistance to erythromycin was 23.0 % (38/165), while resistance to clindamycin was 11.5 % (19/165). Within the latter

Table 4 Comparison of prepartum (35–37 weeks of gestation or ≤ 5 weeks prior to delivery) (A) or optimal prepartum screening (35–37 weeks of gestation or ≤ 5 weeks prior to delivery as well as use of recto-vaginal swabs and selective media) (B) to intrapartum (≤ 7 days prior to delivery) screening

	Intrapartum screening (≤ 7 days prior to delivery)		Total	
	GBS positive	GBS negative		
A. Prepartum screening (35–37 weeks of gestation or ≤ 5 weeks prior to delivery)				
GBS positive	44	13	57	PPV 77.2 %
GBS negative	18	214	232	NPV 92.2 %
Total	62	227	289	
	Sensitivity 71.0 %		Specificity 94.3 %	
B. Optimal prepartum screening (35–37 weeks of gestation or ≤ 5 weeks prior to delivery and use of RVS and selective media)				
GBS positive	41	5	46	PPV 89.1 %
GBS negative	8	90	98	NPV 91.2 %
Total	49	95	144	
	Sensitivity 83.7 %		Specificity 91.8 %	

RVS recto-vaginal swab, PPV positive predictive value, NPV negative predictive value

category, inducible clindamycin resistance was 6.1 % (10/165). Rates of erythromycin resistance in neonatal isolates were higher (i.e., 32.0 %, 8/25) than in pregnant women (i.e., 21.4 % [30/140]), although the difference was not deemed statistically significant (data not shown). No erythromycin was given for IAP.

Capsular types

The four most common capsular types, both in neonatal and in pregnant women's isolates, were types Ia, II, III, and V (Fig. 1). Together, they accounted for 86.7 % (143/165) of all isolates. In neonates, type III strains seemed to be predominant (i.e., 40.0 % in neonates vs. 25.7 % in pregnant women), but the difference did not reach statistical significance (data not shown). Type IV, VI, and VII strains were seen only in colonized mothers.

There was full agreement between serotyping and genotyping results for types Ia, Ib, and II–VII strains. Type VIII was absent. GBS strains that were serotyped as type IX were all reclassified by genotyping (1 \times type Ia, 2 \times type V; Table 5), because the specificity of type IX serum in the STREP B-Latex kit is known to be too low, which requires positive serotyping results to be confirmed by more accurate genotyping [1]. All non-typeable strains by antisera were able to be typed by PCR (Table 5).

When comparing 14 GBS pairs from mothers and infants, all 14 isolates were found to be of the same capsular type (4 \times type Ia, 2 \times type II, 6 \times type III, 2 \times type V).

Discussion

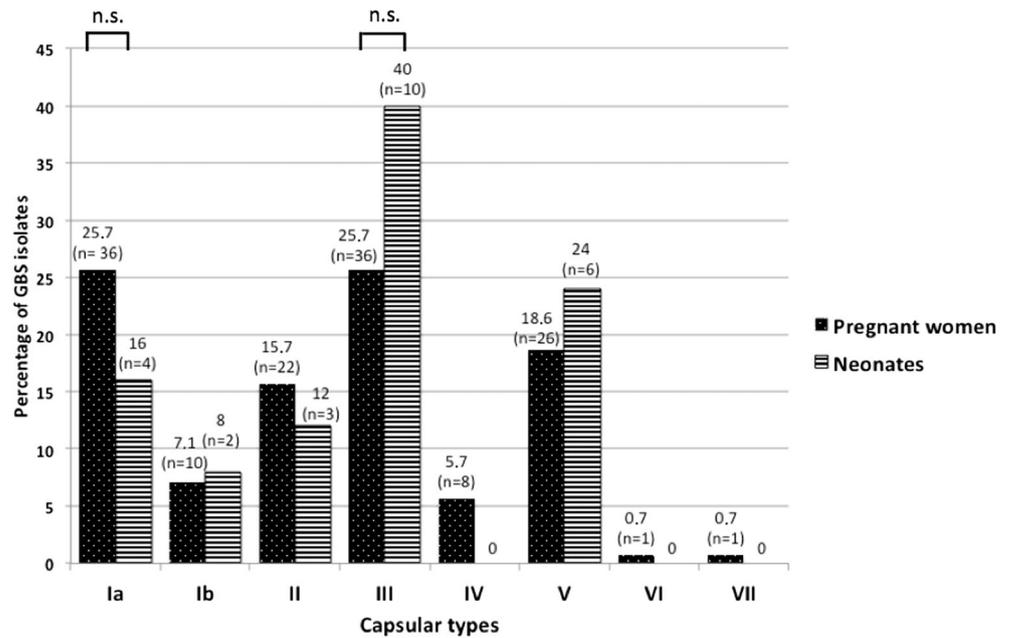
We examined epidemiological trends of GBS in pregnant women and their infants in a tertiary care center in Germany.

GBS colonization rates in pregnant women during weeks 35–37 of gestation were shown to be 18.5 %. This figure is comparable to the 21 % colonization rate documented in an earlier GBS study at the same hospital—a study conducted with a similar design during 2003–2004 [14]. These figures lie within the range of the 10–35 % that previously have been described in studies from Germany and other parts of the world [5, 16].

In our current study, the prenatal GBS screening participation rate was 68.1 %. This rate is considerably lower than that reported from the USA during 2003–2004 (85 %) [24] or that reported from France during 2009 (96.3 %) [7]. Not only a low acceptance rate but also poor adherence to recommended guidelines were documented in our study. Overall, only 22.7 % of screenings were in full compliance with guideline recommendations. This number proved to be even lower when screening was performed by gynecologists in private practice (i.e., 3.1 %). Despite being recommended by national and international medical societies, GBS screening in Germany is not reimbursed by the German health insurance system. As a result, patients must pay out of pocket for GBS screening. We surmise that this has had an ongoing adverse effect on adoption rates for GBS screening.

A further striking finding of our study is that the colonization rates detected through imperfect prepartum screening were not markedly different from intrapartum screening performed in full compliance with national guidelines. A selective enrichment broth was used in only 29.2 % of prepartum screening, whereas the rate of selective agar plate usage was high (i.e., 94.9 %). Although they are based on small sample size, these findings suggest that—from a practical, clinical perspective—using selective plates may be of greater value than using selective enrichment broth. Significantly, this reduction in screening requirements would lower the cost of GBS screening. Nevertheless, these conclusions should be

Fig. 1 Comparison of capsular types of GBS isolates from pregnant women ($n=140$) with those from infants ($n=25$)



confirmed by means of a prospective—and preferably multi-center—study comparing prepartum screening both with and without selective enrichment media.

With respect to GBS colonization within 7 days of delivery, prepartum screening had a positive predictive value (PPV) of 77.2 % and a negative predictive value (NPV) of 92.2 %. During the time our study was being conducted, Lin et al. published results from a study with a similar study design to ours [15]: GBS carriage at delivery was 18.8 % as compared to 24.5 % at prenatal screen. PPV and NPV were reported to be 50.5 and 91.7 %, respectively [15]. Our results, together with those from Lin et al. [15], are within the expected range of 43–100 % (mean 69 %) for PPV and 80–100 % (mean 94 %) for NPV [23, 27].

GBS transmission risk is directly related to density of GBS colonization within 7 days of delivery [4]. A density of more than 100 colonies per 10 μ l was associated with a statistically higher risk of GBS transmission to the infant than a colonization density of <50 colonies per 10 μ l. This finding is in agreement with those from Ancona et al. [2], who showed that 73 % of their infants colonized on day 1 of life were born to mothers with high GBS density. However, when their infants were swabbed a second time before hospital discharge, nearly half of the continuously GBS-colonized infants were shown to have been born to mothers with low or moderate GBS density, indicating that density mainly plays a role in early GBS transmission. Unfortunately, our study was not specifically designed to differentiate between early and late neonatal

Table 5 Comparison of capsular serotypes to genotypes of all GBS isolates ($n=165$)

Capsular genotype	Capsular serotype										n.t.	Total
	Ia	Ib	II	III	IV	V	VI	VII	VIII	IX		
Ia	30	0	0	0	0	0	0	0	0	0	10	40
Ib	0	11	0	0	0	0	0	0	0	1	0	12
II	0	0	21	0	0	0	0	0	0	0	4	25
III	0	0	0	45	0	0	0	0	0	0	1	46
IV	0	0	0	0	5	0	0	0	0	0	3	8
V	0	0	0	0	0	28	0	0	0	2	2	32
VI	0	0	0	0	0	0	1	0	0	0	0	1
VII	0	0	0	0	0	0	0	1	0	0	0	1
VIII	0	0	0	0	0	0	0	0	0	0	0	0
IX	0	0	0	0	0	0	0	0	0	0	0	0
n.t.	0	0	0	0	0	0	0	0	0	0	0	0
Total	30	11	21	45	5	28	1	1	0	3	20	165

Numbers in italics concordance between serotyping and genotyping

n.t. non-typeable

transmission. For this reason, we were not able to evaluate the influence of GBS density on the risk of vertical transmission.

During 2011–2012, the overall IAP rate at our hospital rose to 89.3 % of women who had a positive prepartum GBS screen. However, the optimal IAP—i.e., start of IAP at least 4 h prior to delivery—still has experienced only a moderate increase: from 38.8 % in 2003–2004 [14] to 57.1 % in our current study. Nevertheless, in interpreting these data, we must take into consideration that culture results from the intrapartum screening were not always available within 4 h of delivery. Besides additional educational interventions, a faster but still reliable screening test for GBS—preferably a point-of-care test—clearly would be of value in improving the IAP rate.

At our institution, no antibiotic resistance to penicillins and cephalosporins has been noted. However, between the time of our previous study in 2003–2004 and that of our current study, the clindamycin resistance rates increased from 7.7 [14] to 11.5 %, and for erythromycin from 11.0 [14] to 23.0 %. Globally, up to 25 % of GBS isolates are clindamycin-resistant [17]. Clindamycin should be used only if inducible clindamycin resistance can be excluded by the microbiology laboratory [25].

The overall distribution of capsular types in our current cohort was comparable to that of the earlier study cohort. The four most common capsular types were types Ia, II, III, and V, which together accounted for 86.7 % in the current cohort and 90.6 % (163/180) in the 2003–2004 cohort [14]. Within the four major capsular types, minor changes occurred, primarily involving an increase of type Ia isolates (data not shown). In both our studies, the number of GBS strains serotyped was relatively small, thus requiring cautious interpretation. However, this distribution of isolates is similar to that described in the literature [8, 19]. In both of our studies, the predominant isolate was type III, especially among neonatal isolates. Furthermore, type III strains accounted for two thirds of invasive GBS disease in neonates in a German-wide surveillance study [10]. The same predominance of type III holds true globally as well [8, 13]. The higher density of type III strains in pregnant women may favor type III transmission. In fact, mothers who passed on type III GBS to their infants had the highest rates of 3+ density (4/5 in type III vs. 4/8 in non-type III). For these reasons, it would be of high interest to identify GBS clones that harbor an increased risk for transmission and invasive disease. Doing so could allow for the development of a more focused prophylaxis strategy that could reduce the quantity of antibiotics given during labor and delivery. One such preventive approach would be the development of a GBS vaccine [11, 16]. The most advanced vaccine candidates are based upon GBS capsular polysaccharides [11, 16, 18]. The stable distribution of capsular types in our cohort is encouraging for the potential efficacy of a conjugated capsular polysaccharide vaccine.

The primary limitation of our study revolves around its design as a single-center study at a tertiary care center, a fact which implicates potential selection biases. In addition, the small number of GBS-colonized infants underpowered the effect that GBS screening and IAP had on GBS transmission. The relatively low transmission rate in our study may be related to our not having included rectal swabs from infants, another active replication site for GBS colonization. However, our study results are strengthened by the fact that trends documented were able to be analyzed in direct comparison with results from a study with a very similar design performed a decade previously at the same hospital. By contrast, in multi-center studies, an analysis of trends and/or their implications is rarely able to be the focus.

In conclusion, our study documents acceptance of prepartum GBS screening in Germany to be lower than in other European and North American countries. There is a clear need to improve participation rates in Germany. Our study suggests that not using a selective enrichment broth in the screening protocol may not have negative effects on screening efficacies and could thereby lower screening-related costs. Further, the capsular serotype pattern of colonizing GBS strains in Germany has remained stable over the past decade. A tetravalent GBS vaccine directed against capsular types Ia, II, III, and V would cover almost 90 % of all colonizing GBS strains. Most importantly, development of such a vaccine could significantly reduce the burden of neonatal GBS disease.

Acknowledgments RE is a recipient of a postdoctoral research fellowship from the German Research Foundation (DFG EL 790/1-1)

Compliance with ethical standards

Conflict of interest The authors have no funding or conflicts of interest to disclose.

Integrity of research and reporting This study was approved by the ethics committee of Freiburg Medical Center Freiburg and therefore has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All study participants gave their informed consent prior to their inclusion in the study. No details that might disclose the identity of study participants are given in the manuscript.

Contributor's statement Mirjam Kunze conceived and designed the study, collected the data, contributed to the interpretation of the data, drafted the manuscript, and approved the final manuscript as submitted.

Katharina Zumstein contributed to the study design and interpretation of the data, collected the data, contributed to the statistical analysis, and approved the final manuscript as submitted.

Filiz Markfeld-Erol collected the data and approved the final manuscript as submitted.

Roland Elling contributed to the study design and interpretation of the data and approved the final manuscript as submitted.

Fabian Lander collected the data, contributed to the microbiological analysis of samples, and approved the final manuscript as submitted.

Heinrich Prömpeler contributed to the study design and interpretation of the data and approved the final version of the manuscript as submitted.

Reinhard Berner conceived and designed the study, contributed to the interpretation of the data, and approved the final manuscript as submitted.

Markus Hufnagel conceived and designed the study, contributed to the interpretation of the data, performed the statistical analysis, drafted the manuscript, and approved the final manuscript as submitted.

References

- Afshar B, Broughton K, Creti R, Decheva A, Hufnagel M, Kriz P, Lambertsen L, Lovgren M, Melin P, Orefici G, Poyart C, Radtke A, Rodriguez-Granger J, Sørensen UB, Telford J, Valinsky L, Zachariadou L, Members of the DEVANI Study Group, Efstratiou A (2011) International external quality assurance for laboratory identification and typing of *Streptococcus agalactiae* (group B streptococci). *J Clin Microbiol* 49:1475–1482
- Ancona RJ, Ferrieri P, Williams PP (1980) Maternal factors that enhance the acquisition of group-B streptococci by newborn infants. *J Med Microbiol* 13:273–280
- AWMF-Leitlinie (2008) Prophylaxe der Neugeborenen-sepsis – frühe Form – durch Streptokokken der Gruppe B. AWMF-Leitlinien-Register N2. 024/020. 1996. Last update 07/2008. Available at: <http://www.dgpi.de/publikationen/awmf>. Accessed 15 Nov 2014
- Benitz WE, Gould JB, Druzin ML (1999) Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. *Pediatrics* 103:e77
- Brimil N, Barthell E, Heindrichs U, Kuhn M, Lütticken R, Spellerberg B (2006) Epidemiology of *Streptococcus agalactiae* colonization in Germany. *Int J Med Microbiol* 296:39–44
- CDC (1996) Prevention of perinatal group B streptococcal disease: a public health perspective. *MMWR Recomm Rep* 45(RR-7):1–24
- Corte M, Dupont C, Prunaret-Julien V, Fernandez MP, Peigne E, Huissoud C, Rudigoz RC, Aurore G (2010) Evolution of adherence to guidelines for prevention of group B streptococcal infections. *J Gynecol Obstet Biol Reprod* 39:569–574
- Edmond KM, Kortsalioudaki C, Scott S, Schrag SJ, Uaidi AKM, Cousens S, Heath P (2012) Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet* 379:547–556
- EUCAST (2012) 2012 European Committee on Antimicrobial Susceptibility Testing—breakpoint tables for interpretation of MICs and zone diameters. Available at: http://www.eucast.org/antimicrobial_susceptibility_testing/previous_versions_of_tables/. Accessed 30 March 2014
- Fluegge K, Siedler A, Heinrich B, Schulte-Moenting J, Moennig MJ, Bartels DB, Dammann O, von Kries R, Berner R, German Pediatric Surveillance Unit Study Group (2006) Incidence and clinical presentation of invasive neonatal group B streptococcal infections in Germany. *Pediatrics* 117:e1139–e1145
- Heath PT (2011) An update on vaccination against group B streptococcus. *Expert Rev Vaccines* 10:685–694
- Imperi M, Pataracchia M, Alfàrone G, Baldassarri L, Orefici G, Creti R (2010) A multiplex PCR assay for the direct identification of the capsular type (Ia to IX) of *Streptococcus agalactiae*. *J Microbiol Methods* 80:212–214
- Johri AK, Paoletti LC, Glaser P, Dua M, Sharma PK, Grandi G, Rappuoli R (2006) Group B *Streptococcus*: global incidence and vaccine development. *Nat Rev Microbiol* 4:932–942
- Kunze M, Ziegler A, Fluegge K, Hentschel R, Proempeler H, Berner R (2011) Colonization, serotypes and transmission rates of Group B streptococci in pregnant women and their infants born at a single University Center in Germany. *J Perinat Med* 39:417–422
- Lin FYC, Weisman LE, Azimi P, Young AE, Chang K, Cielo M, Moyer P, Troendle JF, Schneerson R, Robbins JB (2011) Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B streptococcal disease. *Pediatr Infect Dis J* 30:759–763
- Melin P (2011) Neonatal group B streptococcal disease: from pathogenesis to preventive strategies. *Clin Microbiol Infect* 17:1294–1303
- Randis TM, Polin RA (2010) Early-onset group B streptococcal sepsis: new recommendations from the Centres for Disease Control and Prevention. *Arch Dis Child Fetal Neonatal Ed* 97:F291–F294
- Rodriguez-Granger J, Alvargonzalez JC, Berardi A, Berner R, Kunze M, Hufnagel M, Melin P, Decheva A, Orefici G, Poyart C, Telford J, Efstratiou A, Killian M, Krizova P, Baldassarri L, Spellerberg B, Puertas A, Rosa-Fraile M (2012) Prevention of group B streptococcal diseases revisited. The DEVANI European project. *Eur J Clin Microbiol Infect Dis* 31:2097–2104
- Savoia D, Gottimer C, Crocilla C, Zucca M (2008) *Streptococcus agalactiae* in pregnant women. Phenotypic and genotypic characters. *J Infect* 56:120–125
- Schrag SJ, Gorwitz R, Fultz-Butts K, Schuchat A (2002) Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep* 51:1–22
- Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, Hadler JL, Danila R, Cieslak PR, Schuchat A (2000) Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 342:15–20
- Schuchat A (2001) Group B Streptococcal disease: from trials and tribulations to triumph and trepidation. *Clin Infect Dis* 33:751–756
- Valkenburg-van den Berg AW, Houtman-Roelofs RL, Oostvogel PM, Dekker FW, Dörr PJ, Spij AJ (2010) Timing of group B streptococcus screening in pregnancy: a systematic review. *Gynecol Obstet Investig* 69:174–183
- Van Dyke MK, Phares CR, Lynfield R, Thomas AR, Arnold KE, Craig AS (2009) Evaluation of universal antenatal screening for group B streptococcus. *N Engl J Med* 360:2626–2636
- Verani JR, McGee L, Schrag SJ (2010) Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep* 59:1–36
- Wald ER, Dashefsky B, Green M, Harger J, Parise M, Korey C, Beyers C (1987) Rapid detection of group B streptococci directly from vaginal swabs. *J Clin Microbiol* 25:573–574
- Yancey MK, Schuchat A, Brwon LK, Ventura VL, Markenson GR (1996) The accuracy of late antenatal screening cultures in predicting genital group B streptococcal colonization at delivery. *Obstet Gynecol* 88:811–815