

# Barriers to the efficient implementation of the neonatal Group B Streptococcal (GBS) disease prevention programme. A retrospective documentation analysis, eastern Croatia

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## Research

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# Abstract

**Objectives.** To analyse the implementation status of the neonatal Group B Streptococcal (GBS) disease prevention programme in the town of Osijek area, eastern Croatia.

**Methods.** A retrospective analysis of archive documentation on an annual basis (2016). A conversation with gynaecologists was conducted to complement this analysis.

**Results.** There was a prevalent proportion of the GBS swab culture findings (3/4) of cervical origin, as gynaecologists use this technique in a wide range of risk conditions related to pregnancy and as a screening technique, as well. The universal screening was performed in almost every second pregnant women (44.7%). This proportion could be a higher, counting on that the cervical swab sampling is customised among gynaecologists. The approximate prevalence of maternal GBS colonisation was above 6%. The prevalence of neonatal sepsis was 6.46%. In a major part of new-borns with sepsis, the infectious agent was unknown (92%). The GBS caused sepsis was found in 7 (5%) cases. Infectious agents other than GBS were found in 4 (3%) cases.

**Conclusions.** The problem oriented hospital documentation, supported by the ICT system, is a prerequisite for a continuous monitoring of implementation of the neonatal GBS disease prevention programme.

## Introduction

Group B Streptococcus (GBS) has emerged in the 1970s as a leading cause of early neonatal infections in many developed countries (1). GBS is a part of normal flora of the female urogenital tract and rectum (2). Epidemiologic studies indicated that approximately 10%-40% of pregnant women carry GBS in their vagina and rectum (3). In developing countries, the prevalence of GBS colonisation in vagina and rectum of pregnant women was reported to range from 8.5–22% (4). A recent review documented worldwide variations in the GBS colonization rate, with values of 10–30% in the United States, 6.5–36% in Europe, 7.1–16% in Asia, 9.1–25.3% in the Middle East, and 11.9–31.6% in Africa (5). These discrepancies might be due to variations in demographic characteristics, geographic locations, and services availability, as described in reports from elsewhere in the world (6). The GBS colonization is clinically important, as there can be a vertical transfer of GBS during the delivery of neonates, causing sepsis and meningitis in neonates and young infants, and leading to the serious infections in women during the gestational and postpartum period (2).

There is a distinct difference between the early onset disease, which occurs in the first 7 days of life (7) and the late onset disease, which is manifested with pneumonia, meningitis, and sepsis, and carries a mortality rate of up to 20% (8). The early onset disease is a target for the antenatal screening programme; the main risk factor is intrapartum vaginal colonisation, usually with GBS, delivered from the gastrointestinal tract of a mother (9, 10). The contributing factors are: preterm delivery, maternal fever during delivery, membranes rupture for more than 18 hours, GBS bacteria detected during pregnancy, and

neonates with GBS infection in past deliveries (11, 12). The late onset disease, on the contrary, is considered a consequence of a horizontal infection transmission, and include diverse infectious agents.

Early clinical trials, conducted in the 1980s, showed that intrapartum antibiotic prophylaxis can prevent early onset GBS disease (13). In 1996, the first guidelines were endorsed in the USA (14, 15). Two alternative prevention strategies have been suggested. The first strategy proposes universal screening of GBS colonisation for all pregnant women at 35–37 weeks of gestation, followed by intrapartum antibiotic prophylaxis to colonised mothers. The second strategy proposes the use of the targeted intrapartum antibiotic therapy for pregnant women with obstetric risk factors, regardless of whether antenatal GBS testing has been undertaken or not. Experiences so far have argued in favor of universal screening against the risk based strategy (16). The USA guidelines of neonatal GBS prevention were updated in 2002 to show that universal screening is the most optimal strategy to select pregnant women who would benefit from intrapartum antibiotic therapy (17).

In many other western and EU countries, the national guidelines have subsequently been adopted, but with different prevention policies (18). Experiences showed that regardless of the type of the prevention programmes, their implementation has provided a significant reduction in the incidence of invasive GBS infections (19, 20). Many issues still need to be considered, including microbiological technique performances for more accurate detection of GBS colonisation and infection, routine intrapartum use of the rapid polymerase chain reaction (PCR) test, the real-time GBS detection, GBS vaccines for pregnant women or those who are planning a pregnancy, and issues important for coordination of the prevention policies among EU countries (3, 18).

In 2010, the Centers for Disease Control and Prevention (CDC), in a collaboration with the American College of Obstetricians and Gynecologists (ACOG), issued the third set of the GBS prevention guidelines (21). In 2018, the stewardship for updating the GBS prophylaxis guidelines were transferred from the CDC to the ACOG and the American Academy of Pediatrics. In addition, the American Society of Microbiology has maintained the standards for laboratory procedures relevant to processing of the specimens. This Committee Opinion provides an update of the recommended prophylaxis and prevention strategies for women during pregnancy and labor (14).

In Croatia, the national recommendations for antimicrobial prophylaxis of early onset GBS disease were issued in 2010 (22). They comprise two approaches: the risk factors based approach, and antenatal screening, however not taken as a mandatory measure. The risk factors strategy includes standard risk factors, but also the statement that the intrapartum antibiotic prophylaxis should be given to pregnant women with positive cervical GBS swab culture, if detected during pregnancy, regardless of whether or not pregnant women have been formerly treated with antibiotics, and regardless of post treatment testing results. The rationale for this additional statement is that the positive GBS cervical swab culture is considered a sign of a heavy maternal GBS colonisation.

There are no published papers on Croatian experiences in prevention of neonatal GBS disease, except for a small cross-sectional study conducted in the town of Osijek area, performed several years before the

national recommendations have been issued (23). We used the retrospective data from the hospital archive books to evaluate this issue. The aim was to analyse the implementation status of the neonatal GBS disease prevention programme in the town of Osijek area, eastern Croatia, including the extent to which this program has been implemented, and the patterns of the prevention strategies that have been used in practice.

## Materials And Methods

The maternal GBS colonisation screening and specimen collection procedures, according to how they are performed by gynecologists in the Osijek area, Eastern Croatia.

In pregnant women at 35–37 weeks of gestation, culture is taken from one vaginal and rectal swab (through the anal sphincter) or the perineum. Recent findings recommend sampling from both areas to increase the sensitivity of the detection method (24). Both gynecologists, who are employed in the Obstetrics and Gynaecology Department of the Osijek University Hospital Centre, and those working in Primary Health Care (PHC) and private facilities, are included in the specimen sampling procedure.

The problem, as stated by the gynecologists from the Osijek area, is that many doctors use the old fashioned sampling method. The most of gynecologists still use a single vaginal swab. A part of them yet use anorectal or/and perineal swabs, while only a minority of them use the combined method. Apart from using the isolated vaginal method, gynecologists consider the two latter sampling methods as the unique "vagino-perineal" swab sampling method.

Another peculiarity of the maternal GBS colonisation screening programme in the Osijek area, is that gynecologists perform the cervical swab culture by testing pregnant women with various risk factors, including both, the standard ones, as addressed in the global guidelines, and also those risk factors which are not widely accepted as indications for the intrapartum administration of antibiotics, like hypertension and diabetes, promiscuous behavior, and multiple pregnancies (25, 26, 27). In the Osijek area, the cervical swab culture testing is performed for a wide range of infectious agents, known as being the common causes of cervicitis, which in addition to GBS include *E. Coli*, Enterobacteriaceae, *Ureaplasma urealyticum*, *Mycoplasma genitalium* and *Chlamydia Trachomatis* (28). The urine microbiological culture testing is performed as a part of the same routine procedure. Another situation when gynecologists in the Osijek area routinely perform cervical GBS testing is for non-pregnant women included in the infertility assistance program.

The specimen isolation and identification of the grown bacteria are performed according to the international standards (28). Samples are inoculated into a selective, enriched Todd-Hewitt broth and supplemented with nalidixic acid (15 µg/ml) and colistin (10 µg/ml), then incubated at the body temperature (37°C) and transported to the microbiology laboratory. The next step is isolation of GBS on the subculture, using blood agar plates. The final stage is serologic identification of the GBS strain, using latex agglutination with GBS antisera.

The study protocol: A retrospective epidemiologic study. The data was analysed for one year, taken from the archives and registers of the Microbiology Department at the regional Public Health Institute, the Obstetrics and Gynaecology Department and the Neonatal Intensive Care Unit of the Osijek University Hospital Center. Vaginal and vagino-perineal GBS swab culture samples were analysed at the Microbiology Department of the Public Health Institute, in the period between January and December 2016.

The Information Computer Technology (ICT) system has been installed in the Microbiology Department. The hospital departments are still supplied by the archive books. We searched the ICT register of the Microbiology Department and listed out records related to GBS swab culture testing. Since there was no information on GBS swab specimen origin, we searched through the archive documentation of the Microbiology Department manually, to discern between vaginal, vagino-perineal, and cervical GBS swab culture findings. We took into account documents related to vaginal and vagino-perineal specimens, cervical and posterior fornix swab specimens.

Another necessary information for the estimation of the prevalence of GBS maternal colonisation, was the number of pregnant women in the year for which analysis was performed. We searched manually the archive books the Obstetrics and Gynaecology Department of the Osijek University Hospital Centre, to extract this number. Finally, to determine the number of deliveries which have been complicated with neonatal sepsis or systemic infections, we performed the manual search of the archive books of the Neonatal Intensive Care Unit.

## **Statistical analysis**

Statistical analysis was performed using the statistical package MedCalc ver. 14.12.0, MedCalc Software. Data was processed by the descriptive statistics method. Fisher's exact test and  $\chi^2$  test were used to compare some categorical variables. A p-value less than 0.05 was considered significant. Materials and Methods should be described with sufficient details to allow others to replicate and build on published results. Please note that publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies require ethical approval must list the authority that provided approval and the corresponding ethical approval code.

# Results

In the period for which research was conducted, from the beginning of January to the end of December, 2016, there were in total GBS swab culture findings (3979), all performed at the Microbiology Department. These findings were classified according to the location the sample was taken from (Fig. 1).

A total number of 1023 pregnant women were tested for GBS colonisation using vaginal or vagino-perineal (anorectal/perineal or combined vaginal and anorectal/perineal) swab culture sampling. The number of positive results was 46 (4.5%) (Fig. 1).

The largest number of findings (2827) tested on GBS in 2016, were based on taking the cervical swab, of which 78 (2.76%) were positive. The smallest part of the samples was taken from the fornix of the vagina, of which 4 (3.10%) were positive. Although the largest number of findings were based on taking the cervical swab, the statistically significantly lowest percentage of positive findings used this method ( $p = 0.024$ ; Fisher's exact test). Significantly, most findings were taken by the cervical sample ( $p < 0.001$ ;  $\chi^2$  test) (Fig. 2).

From data used from the archive books of the Osijek University Hospital Centre for the year 2016, we determined the number of women who had deliveries in 2016, in the town of Osijek area (used as an approximation of the total number of pregnant women), the number of women who were or were not screened for GBS colonisation, and the number of screened women tested negative or positive.

The number of women who had deliveries in 2016 was 2290. The proportion between this number and the total number of pregnant women tested on GBS colonisation was 1023/2290 (44.7%), providing the approximate GBS maternal screening rate. Of the total number of women screened on GBS colonisation (1023), there were 46 (4.5%) those who were tested positive (Fig. 3).

There was a total of 148 newborns who in 2016 were hospitalized for sepsis/systemic infections at the Neonatal Intensive Care Unit of the Osijek University Hospital Centre. For the most of them (137 out of 148, or 92%), infectious agents have not been identified. Infectious agents were identified in 11 cases; GBS in 7 (5%) of cases, and other infectious agents in 4 (3%) of cases (Figs. 4 and 5).

# Discussion

We performed the retrospective analysis of the hospital archive documents to gain insights into the implementation status of the GBS neonatal disease prevention programme in our environment (the town of Osijek area, eastern Croatia). This analysis has enabled us information on barriers to the efficient implementation of this programme into practice, and indicated the areas of improvement. A lesson learned from this analysis may be used more generally, to inform the prevention and screening programmes implementation strategies. We identified three problematic areas where improvements are likely to be possible: 1) the inappropriateness of the hospital documentation for the retrospective effectiveness analyses, 2) the discrepancy between the customized protocol performance vs.

recommendations provided by the guidelines, and 3) the difficulties in the guidelines translation into clinical practice. Regarding the appropriateness of the hospital archive documentation, we found that the storage of the archive records is supported by the ICT system only in a part of the hospital facilities. The Department of Gynaecology and Obstetrics and the Neonatal Intensive Care Unit, both departments important for this preventive programme implementation, have not been covered by the ICT system, and the only option for us, to get some relevant information, was to manually search through the archive documentation. Even when the ICT system has been installed, as in the Microbiology Department, which in organisation terms was a part of the Public Health Services, the scope of information that was possible to gain from it, was limited, and not appropriate for this purpose, which implied the need for establishing the problem-oriented documentation. For example, from the vast amount of the microbiologic findings that have been available, we could extract the list of names of women to whom the GBS swab cultures were performed in the year of examination, but it was not possible to specify the sites from which the specimens were used, or to make distinctions between the double named logs, with respect to reasons of the repeated referrals. Anyway, we had to turn to the manual searching method. The result of the documentation search in the Microbiology Department was surprising. About two thirds of the total amount of the GBS swab culture findings, that were analysed in the year 2016, were of the cervical origin (2827/3979 or 71.0%), and only a quarter (1023/3979 or 25.7%) was from the vaginal or anorectal/perineal sites, which are sites indicated in the universal neonatal Group B Streptococcal (GBS) disease prevention programme. Information that we also needed, if want to get insights into the efficiency of the GBS neonatal disease prevention programme, was the number of pregnant women in this year. We faced a new problem, by recognising that there is no specific archive book where pregnant women from the town of Osijek area are registered. Moreover, pregnant women are being dispatched at many points of the health care services, including gynecologists in the Osijek University Hospital Centre, and many individual gynaecologists working in PHC service or private facilities. We used the number of women who in 2016 had deliveries in the Osijek University Hospital Centre, as an approximate number, and for this purpose, we had to search the archive books of the Department of Gynaecology and Obstetrics. We used the number of deliveries (N = 2290) and the number of vaginal and anorectal/perineal GBS swab microbiologic findings (N = 1023) to estimate the approximate number of pregnant women who in the year 2016 were undertaken to the antenatal GBS screening programme. The estimated rate (1023/2290 or 44.7%) was lower than in the USA and some developed EU countries, where these rates were reported to be over 80% (29, 30). However, the direct comparison was difficult, because of a wide variation of protocols that have been adopted in particular countries. Moreover, in some countries, this programme has not been implemented at all (18, 31). Another area of concerns, regarding the efficient GBS screening programme implementation, was a discrepancy between the customized protocol performance vs. recommendations provided by the guidelines. As we could find out in conversation with gynecologists at the Department of Gynaecology and Obstetrics, the unusually large proportion of the cervical GBS swab tests, among the total amount of the GBS swab culture findings, could be explained by the fact that gynecologists in the town of Osijek area usually use this technique for the universal GBS screening (that is, in healthy pregnant women), probably as inertia of the high risk screening strategy. Namely, according to the Croatian national recommendations, positive cervical GBS swab tests, when found in pregnant

women regardless of the reasons of referrals, are considered are indications for intrapartum antibiotics administration, even if the antenatal post treatment testing resulted negative. To assess this assumption objectively, we searched a part of the cervical GBS swab findings and their corresponding referrals. This assumption was true, due to the fact that “normal pregnancy” was the dominant diagnosis on these referrals. If taking into account this fact, that means that the GBS screening rate might have been much higher, than the primarily calculated rate of 44.7%, which was based on using only vaginal and vagino-perineal swab specimens for calculation. To assess whether gynecologists in the town of Osijek area also perform vaginal and vagino-perineal swab specimens as a part of the universal screening strategy in pregnant women, we examined a part of these findings and their referrals (613 out of a total of 1023 vaginal and vagino-perineal GBS swab findings, analysed in the Microbiology Department, in 2016). We found that the major reason for testing the pregnant women this way, was screening on GBS vaginal colonisation. There were only a few women with the diagnosis of some pathological conditions, which was usually associated with the repeated testing. Taken together, that means, that gynecologists in our environment use both types of GBS swab specimens, cervical and vaginal/vagino-perineal, as the universal GBS screening strategies. The bias in how gynecologists perceive the guidelines recommendations may be partly due to the fact that the global, international guidelines, are not sufficiently clear in parts related to complications in pregnancy, including conditions such as diabetes, hypertension, bleeding, or multiple pregnancies. For these conditions, there are no clear recommendations for screening on maternal GBS colonisation and intrapartum antibiotic prophylaxis (25, 26, 27). These conditions are also not mentioned in the latest guidelines on prevention of the GBS early-onset disease in newborns, issued by the American College of Obstetricians and Gynecologists (14). For these conditions, gynecologists in our area regularly perform the cervical GBS swab testing and repeat it depending on the antibiotic treatment results. This custom may be a source of the guidelines misunderstanding, as they use the same technique for the universal screening of GBS colonisation in healthy pregnant women. Despite the problem of information extraction from the archive documents, this retrospective evaluation was useful, since it provided many details on the extent to which the GBS neonatal prevention program has been implemented in our area. When taking into account information that gynecologists, as a strategy of the GBS antenatal screening programme, use both techniques, that one based on using the cervical GBS swab culture, and that one based on using vaginal or vagino-perineal swab cultures, then the positive results of these two techniques, counting 2.76% and 4.5%, can give the approximate rate of the maternal GBS colonisation, that in our area would likely to be 6%-7%. This percentage is at a lower part of the range of 6.5% – 36%, found for European countries, and is typical for economically less developed countries (32). Another benefit of the retrospective evaluation of the hospital documentation is that this procedure has enabled identification of information which would be necessary if someone wants to analyse the effectiveness of this prevention programme implementation. We have come to the similar conclusions as some other authors, realizing that this information should include: reasons of referrals (with more details on the diagnosis, on the site where the specimen was taken from, and on whether it is the first or repeated testing, etc.), the history of antibiotics treatment during the pregnancy and the delivery, and the GBS resistance rates to antibiotics) (31). Information which would be necessary to be recorded in the ICT system, to enable the neonatal sepsis data evaluation, is the identification code,



to serve as the link between the names of the mothers and their new-borns. This conclusion is based on the fact that of the total number of new-borns, who were cured for neonatal sepsis in the Neonatal Intensive Care Unit of the Osijek University Hospital Centre, in 2016, only a small part (20 out of 148) had records on the GBS antenatal screening. There was no information on whether the result of this testing was positive or negative. The disparity between the number of mothers who were screened on GBS colonisation and the number of those who were tested positive (5 positive out of 20 screened), implicates the possibility of the transversal infection transmission during the delivery, which justifies the routine intrapartum use of PCR testing (33). Based on the number of new-borns with sepsis, and the number of women who in 2016 had deliveries, it was possible to estimate the approximate prevalence of neonatal sepsis in our area. This prevalence was 6.46%, which was similar to that in the developed EU countries, for the period for which the data in this study has been collected (34). Our main criticism on how documentation in the Neonatal Intensive Care Unit has been conducted, is on insufficient information on the infectious agents, as the causes of sepsis. For the majority of new-borns (137 out of 148, or 92.5%), the infectious agents were unknown, as they were, either not being tested, or if tested, not identified. GBS was recorded as the cause of sepsis in 7 (5%) of new-borns, but the diagnosis was established mostly on the clinical criteria. The common conclusion was that there is a need for a more systematic microbiological testing of new-borns who are suspected on neonatal sepsis, if wanting to monitor the efficiency of the neonatal GBS disease prevention programme implementation. The infectious agents other than the GBS, including *E. coli*, *Candida albicans*, and non-specified *Streptococcus*, were identified in only four (3%) of new-borns with sepsis. Since these infectious agents may indicate both, the late-onset sepsis, or the preterm birth, information on the time of the sepsis onset, or on whether there was the preterm delivery, or not, should be a mandatory in the Neonatal Intensive Care Unit register (33, 35).

## Conclusions

The retrospective analysis of the hospital documentation, as a research method, may reveal many problematic areas in guidelines and real-life workflows, which should be overcome, if medical doctors and policymakers want to efficiently implement prevention and screening programmes. To achieve the full effectiveness of the GBS neonatal disease prevention programme, it is not enough to have organised the universal GBS screening programme, and to strictly follow indications for intrapartum antibiotics administration. What is also necessary, is to implement, and control over time, a series of actions and measures. For their successful implementation, there is a need for establishing the problem oriented documentation, supported by the ICT system.

## Declarations

Availability of supporting data. Due to nature of this study, data is not available to be shared publicly.

Competing interests. The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the

decision to publish the results.

**Authors' contribution.** Z.B and Lj.T.M were responsible for conceptualization and design of the study. M.V, N.V performed the investigation and collected data. In addition, they were responsible for data validation. Z.B and D.H provided participants with data. Lj.T.M supervised the study. Z.B wrote the manuscript. D. H and Lj.T.M reviewed and edited manuscript. All authors have read and agreed on the published version of the manuscript

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**Conflict of Interest:** Authors declare that there is no conflict of interest.

**Ethical Approval:** This article does not contain any studies with human participants and animals performed by any of the author. The study was approved by the Ethics Committee of the Josip Juraj Strossmayer University of Osijek, Faculty of Medicine in Osijek (approval No. 2158-61-07-15-112).

Informed consent statement was signed by patients in the clinic.

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## Figures

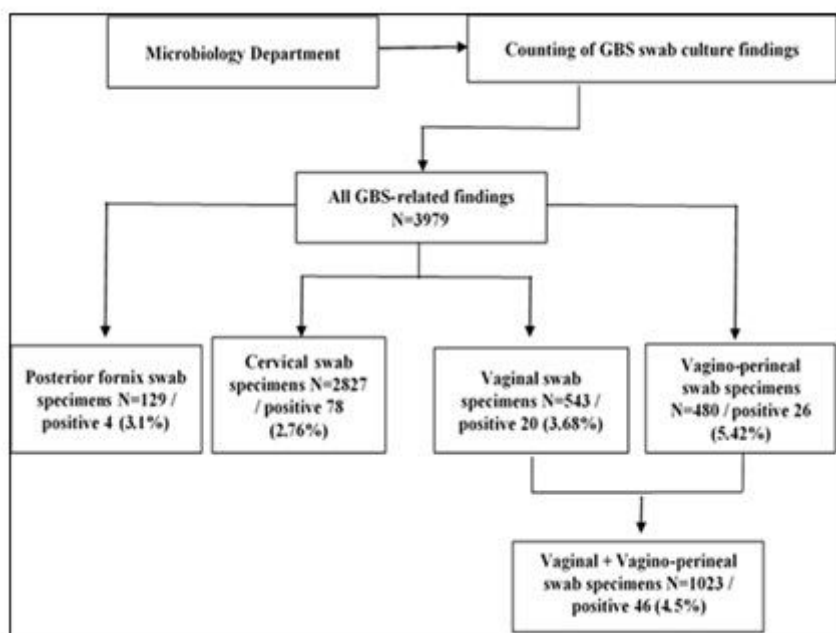
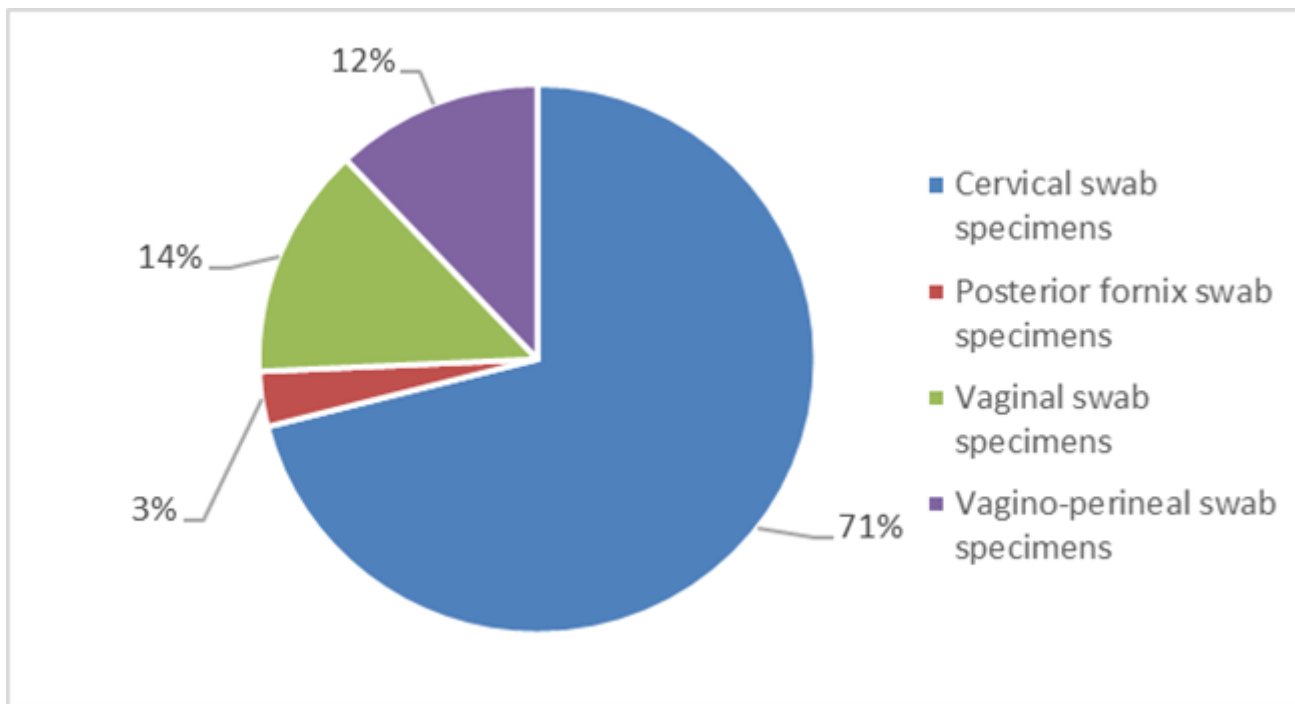


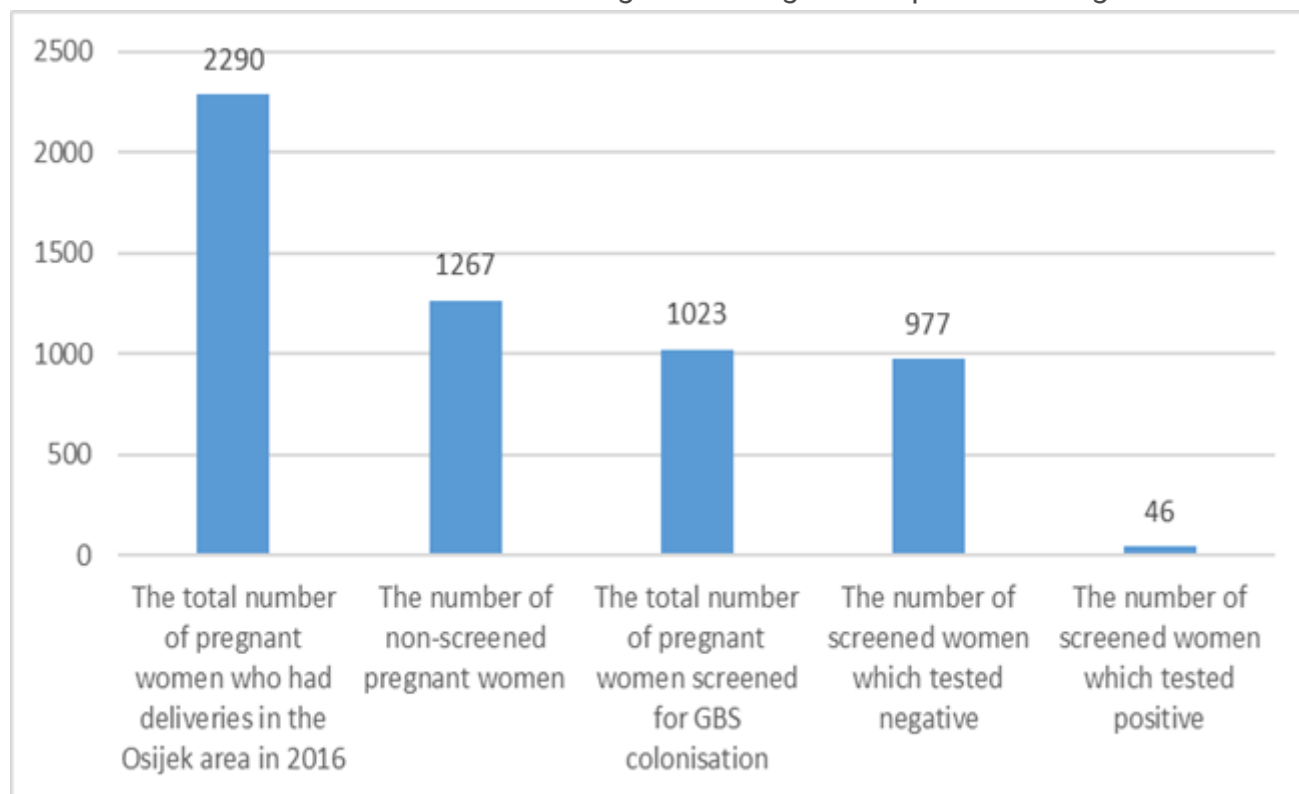
Figure 1

A data source: ICT register of the Microbiology laboratory



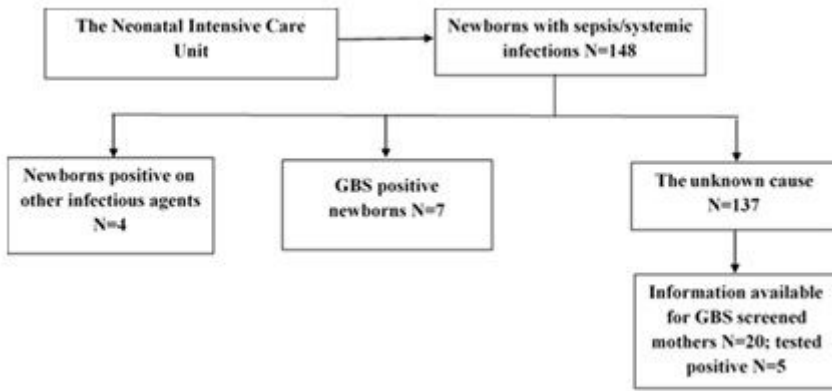
**Figure 2**

The distribution of GBS swab culture findings according to the specimens origin



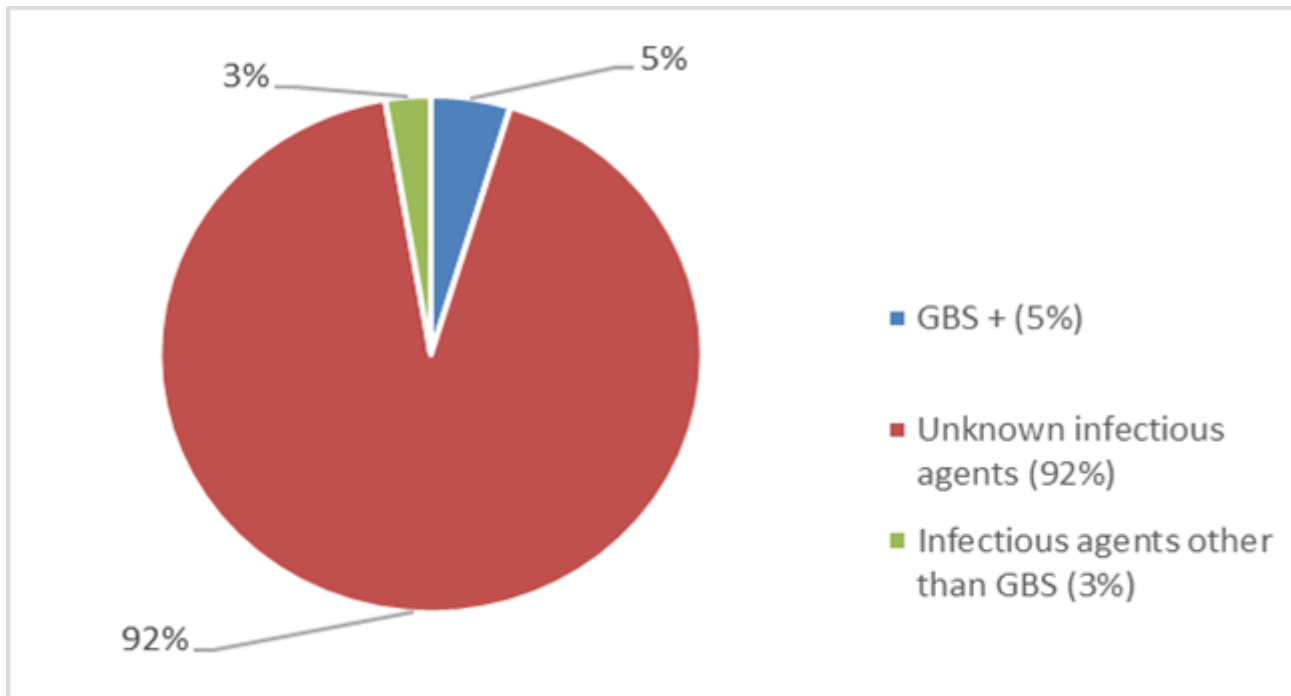
**Figure 3**

Presentation of the total number of births in 2016, the number of untested and the number of tested pregnant women on GBS, and the number of positive and negative findings.



**Figure 4**

The total number of new-borns diagnosed with sepsis/systemic infections in 2016, in the town of Osijek area; the number of those for whom infectious agents were unknown, the number of those who were positive on GBS, and the number of those who were positive on other infectious agents.



**Figure 5**

The distribution of new-borns with sepsis/systemic infections according to the types of infectious agents