DOI: https://doi.org/10.17816/JOWD61875

Russian strains of group B streptococci are different in the content and organization of the PAI-A and PAI-A1 pathogenicity islands

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Group B streptococci, or *Streptococcus agalactiae*, are the major cause of severe diseases in newborns and adults. The PAI-A and PAI-A1 pathogenicity islands containing the *sspB1* and *sspB1a* genes, respectively, were found among group B streptococci mobile genetic elements. The presence of *sspB* genes correlates with urogenital tract infections. The aim of this study was to determine the frequency of group B streptococci strains with the PAI-A and PAI-A1 pathogenicity islands, circulating in Moscow, in comparison with strains from St. Petersburg. The *sspB1* gene, and hence the PAI-A pathogenicity island, was not found in the genomes of strains from Moscow. The frequency of the *sspB1a* gene and the PAI-A1 pathogenicity island in the genomes of clinical strains was three times higher than in the genomes of colonizing strains. Thus, it can be assumed that the genes of the *sspB* family are more specific of group B streptococci colonizing pregnant women and newborns.

Keywords: group B streptococci; PAI-A and PAI-A1 pathogenicity islands; *sspB1* and *sspB1a* genes.

To cite this article:
Kuleshevich EV, Ilyasov YuYu, Linnik DS, Malchenkova AA, Arzhanova ON, Briko NI, Glushkova EV, Priputnevich TV, Suvorov AN. Russian strains of group B streptococci are different in the content and organization of the PAI-A and PAI-A1 pathogenicity islands. *Journal of Obstetrics and Women's Diseases.* 2021;70(4):65–72. DOI: https://doi.org/10.17816/JOWD61875

Received: 25.02.2021 **Accepted:** 30.06.2021 **Published:** 31.08.2021

УДК 616.94-022.7Streptococcus
DOI: https://doi.org/10.17816/JOWD61875

Распространенность островов патогенности PAI-A и PAI-A1 среди российских штаммов стрептококков группы B

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Стрептококки группы B, или *Streptococcus agalactiae*, являются возбудителями тяжелых заболеваний у новорожденных и взрослых. Острова патогенности PAI-A и PAI-A1, содержащие гены *sspB1* и *sspB1a* соответственно, были обнаружены среди мобильных генетических элементов стрептококков группы B. Наличие генов *sspB* коррелирует с инфекциями в урогенитальном тракте. Целью данного исследования явилось определение частоты встречаемости штаммов стрептококков группы B с островами патогенности PAI-A и PAI-A1, циркулирующих в Москве, по сравнению со штаммами из Санкт-Петербурга. Ген *sspB1*, а значит, и остров патогенности PAI-A не были обнаружены в геномах штаммов из Москвы. Частота встречаемости гена *sspB1a* и острова патогенности PAI-A1 в геномах клинических штаммов оказалась в 3 раза выше, чем в геномах колонизирующих штаммов. Таким образом, можно предположить, что гены семейства *sspB* более характерны для стрептококков группы B, колонизирующих беременных и новорожденных.

Ключевые слова: стрептококки группы B; острова патогенности PAI-A и PAI-A1; гены *sspB1* и *sspB1a*.

Как цитировать:
Кулешевич Е.В., Ильясов Ю.Ю., Линник Д.С., Мальченкова А.А., Аржанова О.Н., Брико Н.И., Глушкова Е.В., Припутневич Т.В., Суворов А.Н. Распространенность островов патогенности PAI-A и PAI-A1 среди российских штаммов стрептококков группы B // Журнал акушерства и женских болезней. 2021. Т. 70. № 4. С. 65–72. DOI: https://doi.org/10.17816/JOWD61875

Рукопись получена: 25.02.2021 **Рукопись одобрена:** 30.06.2021 **Опубликована:** 31.08.2021

BACKGROUND

Group B streptococci (GBS) were exclusively considered as causative agents of mastitis in cows for a long time, but later on, were discovered to cause various diseases in humans, affecting a variety of organs and tissues [1].

GBS infection in newborns can have an early (first 6 days of life) and late onset (7 days of life to 3 months). GBS can result in sepsis, pneumonia, and less often meningitis in early onset of infection, whereas late infection can cause meningitis. The GBS infection incidence in newborns accounts for 0.53 cases per 1000 live births, and the mortality rate among the affected is 9.6% [2, 3]. Neonatal diseases caused by GBS are widespread worldwide, and the incidence of GBS colonization in pregnant women ranges from 10% to 30% in the United States of America (USA), 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 [3, 4].

GBS leads to invasive (bloodstream infections, meningitis, osteomyelitis, and endocarditis) and non-invasive infections (bacteriuria, fasciitis, cellulitis, endometritis, and wound infections) in pregnant women and young mothers [4].

In addition, GBS can cause arthritis, endocarditis, pneumonia, and bacteremia, as well as urinary tract, soft tissue, skin, and bone infections in adults. The risk group includes people with weakened immunity and the elderly [4].

Currently, ten serotypes of GBS are known (Ia, Ib, and II–IX). The prevalence and dominance of GBS serotypes vary by geographic region. Thus, serotypes Ia, Ib, II, III, and V prevail among the colonizing strains in the USA and Europe, VI and VIII prevail among the pregnant women in Japan, IV and V prevail among the pregnant women in the UAE and Egypt, respectively. Most cases of late onset meningitis in newborns are caused by serotype III invasive strains, whereas in other cases (not in pregnant women), invasive isolates of serotypes Ia and V dominate. However, recent studies showed that both invasive strains appeared in newborns and adults, as well as colonizing serotype IV strains. In Malaysia, serotype VI was found among the dominant colonizing strains and is the second most common isolate in adults with skin and soft tissue infections caused by GBS. In Egypt, serotype VI is a common colonizing serotype in women. Recently in Central Taiwan, the spread of serotype VI was revealed among colonizing and invasive isolates. Several studies identified sporadic serotype VIII strains both among the colonizing and causative agents of invasive GBS diseases. Serotype V was similarly identified in the USA and Europe [4].

The causative agents of 97% of invasive B-streptococcal infections of newborns in all geographic regions are GBS of five serotypes (Ia, Ib, II, III, and V), dominated by serotype III [5].

Most cases of diseases in adults caused by GBS are caused by serotypes V, Ia, and III [6].

Scientists are developing multicomponent vaccines that will protect against GBS of the predominant serotypes since the distribution of serotypes is different in geographic regions of the world.

The pharmaceutical company, GlaxoSmithKline (GSK), has completed phase I/II clinical trials of the CPS-CRM197 trivalent conjugate vaccine against GBS (serotypes Ia, Ib, and III) and is planning for a pentavalent vaccine clinical trials (serotypes Ia, Ib, II, III, and V) [6].

The pharmaceutical company, Pfizer, also announced a clinical trial of a pentavalent conjugate vaccine (serotypes Ia, Ib, II, III, and V) to assess the safety, tolerance, and immunogenicity [6].

The rapid adaptation of GBS to various ecological niches can be due to many factors of pathogenicity. Some of them are described below.

The Bac protein interacts with the components of the human immune system, such as Fc-fragment of immunoglobulin A and factor H [7].

Lipoprotein ScaAB is involved in the transport of divalent metals and the adhesion process [8].

Serine protease C5a-peptidase cleaves and inactivates the C5a component of human complement [9, 10] and binds fibronectin and promotes bacterial invasion of the epithelial cells [7].

CspA is another serine protease, which cleaves the fibronectin extracellular matrix [11].

The surface protein SspB1 includes α-helical structures, a glucan-binding domain, and an anchoring site in the LPXTG cell wall, which classify this protein as an adhesin. The SspB1a protein is its homolog; its identity at the protein level is 72% [12]. According to the authors, the presence of genes of the *sspB* family does not significantly affect the course of pregnancy but can induce intrauterine infection in the fetus and newborn [13]. These proteins can promote adhesion to the genitourinary tract epithelium. The presence of *sspB* genes correlates with urogenital tract infections [12].

Due to the variability of serotypes in different regions worldwide, creating a universal vaccine is impossible; therefore, the creation of recombinant vaccines based on surface proteins has been initiated.

Thus, the Department of Molecular Microbiology of the Institute of Experimental Medicine has developed pentavalent recombinant and recombinant chimeric vaccines (based on five surface proteins Bac, ScaAB, SspB1, ScpB, and CspA), as well as a live vaccine based on the probiotic strain *Enterococcus faecium* L3 [14–16].

Many factors of GBS pathogenicity are localized on mobile genetic elements; therefore, horizontal gene transfer can contribute to the formation of highly new virulent strains.

Table 1. Primers used to identify the *sspB1* and *sspB1a* genes

Primer name	Primer sequence	Product size, bp	Gene
sspB1971	cgt gat att acg ttt ggc aag a	1536	Surface adhesin *SspB1*
sspB3485	cca gtt cct gaa ccg ata aaa g		
sspB1aF	tgg taa tat tct ccc cct tgg	220	*SspB1a*
sspB1aR	ttg cca gat gaa gca gct att		

At the beginning of the XXI century, 14–15 pathogenicity islands were found in GBS [17, 18].

Pathogenicity islands PAI-A and PAI-A1 containing the *sspB1* and *sspB1a* genes, respectively, were identified among the mobile genetic elements of GBS [19–21].

The incidence of *sspB1* and *sspB1a* genes, and therefore of the pathogenicity islands PAI-A and PAI-A1 in St. Petersburg, is 9% and 29%, respectively [21]. However, analysis of the National Center for Biotechnology Information databases indicates a significantly rarer incidence of the PAI-A island worldwide. Information on the prevalence of the pathogenicity islands under study among GBS of various serotypes in other regions of Russia is unavailable. Evidence is also unavailable in the relationship between the presence of these pathogenicity islands in the genome and the virulence of GBS strains.

Therefore, **this study aimed** to determine the incidence of pathogenicity islands, PAI-A and PAI-A1, among clinical and colonizing strains of GBS.

MATERIALS AND METHODS

Bacterial strains and cultivation conditions

This study included the following strains:

1) 24 strains isolated at the V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology in 2014–2016 (clinical);
2) 43 strains were obtained from the I.M. Sechenov First Moscow State Medical University (Sechenov University) in 1987–1990 (colonizing).

Table 2. Incidence of serotypes (%) in the studied strains of group B streptococci

Serotypes	Colonizing	Clinical
Ia	23	22
Ib	7	4
II	**19***	**8***
III	**0***	**18***
IV	**0***	**18***
V	2	12
VI	0	0
VII	2	1
VIII	**5***	**0***

* Statistically significant differences between the two groups ($p < 0.05$).

The GBS strains were grown in Todd Hewitt Broth (Pronadisa, Spain) overnight at 37°C.

Polymerase chain reaction (PCR)

Deoxyribonucleic acid (DNA) from GBS strains was isolated using the Express-DNA-Bio kit (Alkor Bio, Russia) according to the manufacturer's recommendations.

Amplification was performed in a C1000 apparatus (BioRad, USA) using a two-fold Dream-Taq Green master mix (Thermo Fisher Scientific, Lithuania) according to the manufacturer's recommendations and primers presented in Table 1.

PCR results were evaluated in 1% agarose gel supplemented with ethidium bromide using ×1 TAE buffer. The results were visualized in a VersaDoc transilluminator.

Multiplex PCR

Multiplex PCR was used to identify the type of GBS by the polysaccharide capsule nature [22].

Statistical analysis

The significance of differences between collections was assessed using Fisher's exact test. Therefore, we used an online program at the website https://molbiol.kirov.ru/utilites/multitool/.

RESULTS AND DISCUSSION

Determination of serotypes in the studied strains of GBS

Multiplex PCR was conducted to determine the genes of the capsular operon from the DNA of the strains described above to investigate the prevalence of GBS serotypes in various population groups [22]. The serotype of one strain from the Kulakov Institute and 18 strains from the Sechenov University could not be determined by this method. The group of clinical strains also included the previously analyzed GBS strains isolated at the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology, and Reproductology (173 strains) and the Mechnikov North-Western State Medical University (1 strain) [21, 23]. The results are presented in Table 2.

Among the colonizing strains, serotypes Ia, II, and Ib dominate, whereas, among the clinical ones, Ia, II, III, IV, and V serotypes are predominant. Serotypes VII and VIII, rare for Russia, were revealed in both collections.

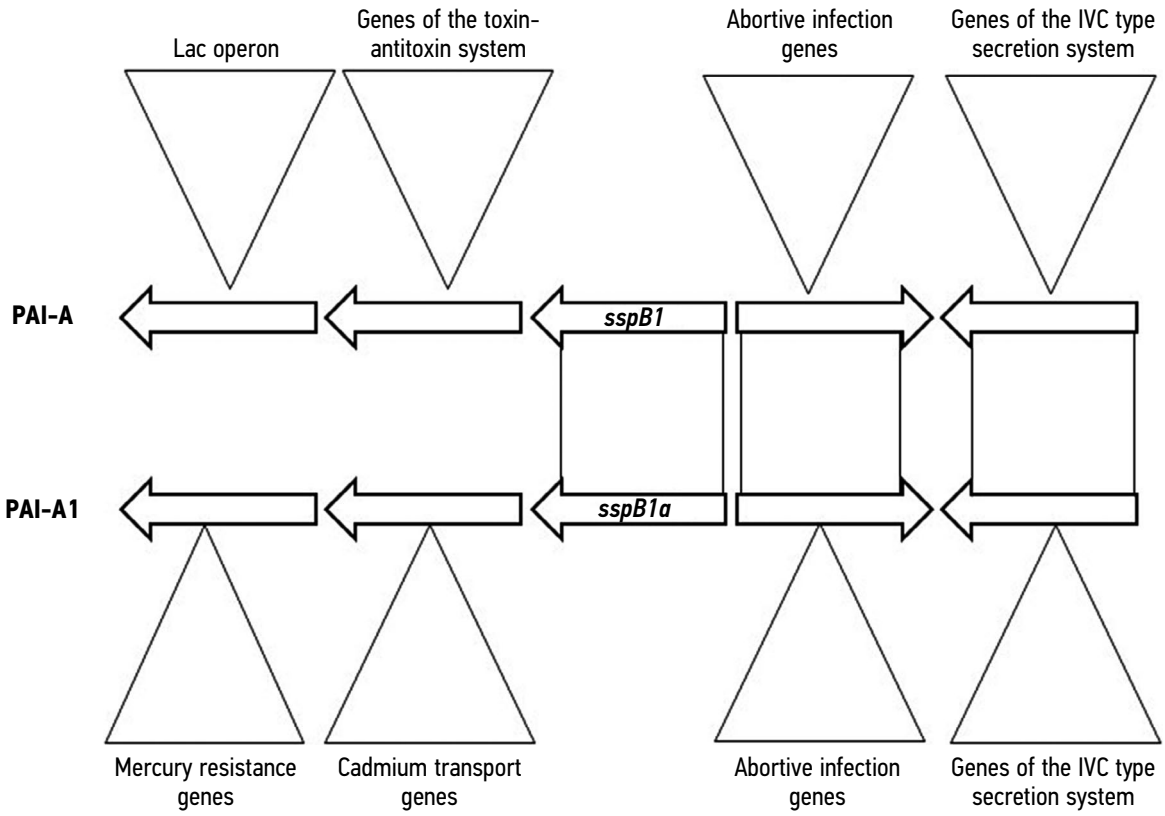

Fig. 1. The structure of the PAI-A and PAI-A1 pathogenicity islands of group B *Streptococci*. Vertical lines indicate homologous areas

Thus, serotype Ia predominates in both collections, serotypes II and VIII are more common in colonizing strains, whereas serotypes III and IV are characteristic only for strains isolated from pregnant women and newborns. Obtained results correspond to the literature data, which state that the predominant serotypes in all geographic regions are Ia, Ib, II, III, and V. The comparison of strains within the collection of clinical strains established that serotype IV is more typical for strains from St. Petersburg and serotype III is more characteristic for strains from Moscow.

Incidence of pathogenicity islands PAI-A and PAI-A1 of GBS associated with genes sspB1 and sspB1a

Two homologous islands of pathogenicity, PAI-A and PAI-A1, were revealed in the genome of GBS strains [21]. The structure of pathogenicity islands is presented in Figure 1.

PCR was performed for the *sspB1* and *sspB1a* genes, which are marker genes of the pathogenicity islands described above to determine the incidence of these mobile genetic elements. The *sspB1* and *sspB1a* genes were previously established to localize in the genomes of 9% and 29% of strains from St. Petersburg, respectively [21]. Figure 2 presents the PCR results with the DNA of clinical strains for the *sspB1a* gene.

The *sspB1* gene was revealed in the genomes of 8% of clinical strains. However, strains with the *sspB1* gene were absent in the strains from Moscow (Table 3). Consequently,

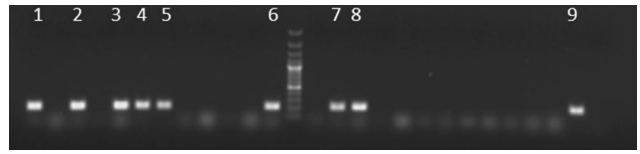

Fig. 2. Electropherogram of the polymerase chain reaction products with clinical strains for the *sspB1a* gene: 1 — strain 2978, 2 — strain 3093, 3 — strain 2828, 4 — strain 3481, 5 — strain 3482, 6 — strain 2698, 7 — strain 3085, 8 — strain 3030, 9 — positive control

strains of GBS with a PAI-A island of pathogenicity circulate mainly in St. Petersburg.

PCR results revealed that the *sspB1a* gene is found in the genomes of 30% of clinical strains and 9% of colonizing strains. The *sspB1a* gene is more often revealed in the genomes of clinical strains, as opposed to colonizing ones.

Thus, it can be assumed that the genes of the *sspB* family are more typical for GBS colonizing pregnant women and newborns.

Table 3. Incidence of *sspB1* and *sspB1a* genes (%) in the studied strains of group B streptococci

Genes	Colonizing	Clinical
sspB1	0	8
sspB1a	**9***	**30***

* statistically significant differences between the two groups ($p < 0.05$).

CONCLUSION

The predominant serotypes among clinical and colonizing strains of GBS correspond to the prevalence data for serotypes worldwide.

The GBS strains with the PAI-A pathogenicity island in their genomes circulate mainly in St. Petersburg.

The homologous pathogenicity island PAI-A1 is characterized by a higher prevalence, as the incidence of this mobile genetic element is three times higher in clinical GBS strains compared to colonizing strains.

The higher prevalence of genes of the *sspB* family among the genomes of clinical strains is of great importance since the SspB1 protein is included in the vaccine against GBS. Since the homology of SspB1 and SspB1a proteins is 72%, the vaccine is possible to act on strains with the *sspB1a* gene.

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.

Funding. This study was supported by the budgetary funds of the Institute of Experimental Medicine (code 0557-20190002, registration number R&D AAAA-A19-119022290066-6).

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