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Molecular genetic characteristics of *Streptococcus pneumoniae* serogroups 15 and 11 representatives circulating in Russia and their relationship with global genetic lineages

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Abstract

Aim of the study. Genetic analysis of *Streptococcus pneumoniae* serogroups 15 and 11 circulating in Russia according to the following parameters: serotype affiliation; clonal complex (CC); presence of resistance and virulence determinants; relatedness to genetic lineages circulating in the world, and justification of inclusion of the actual serotypes of serogroups 15 and 11 in the future conjugate vaccine composition.

Materials and methods. The study included whole genome data of *S. pneumoniae* serogroups 11 and 15.

Results. Genomes of serogroup 15 strains from Russia are represented mainly by serotypes 15B and 15C, the majority of which belong to CC-1025 and CC-1262. CC-1025 is characterized by a more frequent association with invasive diseases. Representatives of CC-1025 and CC-1262 contain virulence determinants unique to these genetic lineages within the studied population of serogroup 15: oligopeptide transporters, fructose-specific PTS system, unique hydrolase variants, additional iron ion transporters, the gene of zinc metalloprotease ZmpC (activating human MMP9). The genomes of serogroup 11 are represented mainly by serotype 11A, the majority belong to CC-62 and CC-1012. The virulence determinants unique to CC-62 (within the studied serogroup 11) include bacteriocins, components of oligopeptide transport, flavin reductase-like protein (adhesin, also protects bacteria from oxidative stress), fucose processing operon, PsaA (adhesin, also a component of the ATP-binding cassette transporter that imports manganese ions).

Conclusion. In the Russian Federation, serogroups 15 and 11 are the most common non-vaccine serogroups. No antimicrobial resistance determinants have been identified in the genomes of representatives of these serogroups. For each of the genetic lineages prevalent in Russia and associated with serogroups 15 and 11, unique virulence determinants within the studied serogroup have been identified, which may contribute to the success of these lineages. It is advisable to include serotypes 15B and 11A in vaccines promising for the Russian Federation.

Keywords: *Streptococcus pneumoniae, serogroups 11 and 15, sequence types, genetic lineages, vaccination, virulence.*

Ethics approval. The study was conducted with the informed consent of the patients or their legal representatives. The research protocol was approved by the Ethics Committee of the SAPIENS (protocol 3.1, January 27, 2020).

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Оригинальное исследование
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Молекулярно-генетическая характеристика *Streptococcus pneumoniae* серогрупп 15 и 11, циркулирующих в России, и их связь с глобальными генетическими линиями

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Аннотация

Цели исследования — генетический анализ *Streptococcus pneumoniae* серогрупп 15 и 11, циркулирующих в России, по параметрам: серотиповая принадлежность; клональный комплекс (CC); наличие детерминант резистентности и вирулентности; взаимосвязь с циркулирующими в мире генетическими линиями; наличие уникальных генов, значимых для проявления вирулентности; обоснование актуальных серотипов серогрупп 15 и 11 для включения в состав будущей конъюгированной вакцины.

Материалы и методы. В исследование включены полногеномные данные *S. pneumoniae* серогрупп 11 и 15.

Результаты. Российские геномы серогруппы 15 представлены в основном серотипами 15B и 15C, большинство относится к CC-1025, CC-1262. Для CC-1025 характерна более частая ассоциация с инвазивными заболеваниями. Представители CC-1025 и CC-1262 содержат уникальные для данных генетических линий, в пределах изучаемой популяции серогруппы 15, детерминанты вирулентности: транспортеры олигопептидов, фруктозоспецифичную фосфотрансферазную транспортную систему, уникальные варианты гидролаз, дополнительные транспортеры ионов железа, ген цинковой металлопротеазы ZmpC (активирующей матриксную металлопротеиназу 9 человека). Геномы серогруппы 11 представлены в основном серотипом 11A, большинство относится к CC-62 и CC-1012. К уникальным для CC-62 детерминантам вирулентности (в пределах изучаемой серогруппы 11) относятся бактериоцины, компоненты транспорта олигопептидов, флавинредуктазаподобный белок (адгезин, также защищает бактерии от окислительного стресса), оперон процессинга фукозы, PsaA (адгезин, также является компонентом АТФ-связывающего кассетного транспортера, импортирующего ионы марганца).

Выводы. В России среди невакцинных серогрупп распространены серогруппы 15 и 11. В геномах представителей этих серогрупп детерминант антимикробной резистентности не выявлено. Для каждой из распространённых в России генетических линий, ассоциированных с серогруппами 15 и 11, идентифицированы уникальные в пределах изучаемой серогруппы детерминанты вирулентности, которые могут способствовать успешности данных линий. В перспективные для России вакцины целесообразно включение серотипов 15B и 11A.

Ключевые слова: *Streptococcus pneumoniae, серогруппы 11 и 15, сиквенс-типы, генетические линии, вакцинация, вирулентность*

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Invasive pneumococcal diseases (pneumonia, meningitis and sepsis) are the most common cause of mortality among children under 5 years of age and adults against the background of reduced immune defense [1, 2].

More than 100 serotypes of *Streptococcus pneumoniae* are known, some of which are highly virulent and capable of causing invasive pneumococcal infection. After the introduction of pneumococcal vaccination with conjugated polysaccharide vaccines into national childhood immunization programs, the previously widespread serotypes have been replaced by non-vaccine serotypes [3]. Two conjugated polysaccharide vaccines are approved for use in Russia: 10-valent (Synflorix, GlaxoSmithKline) and 13-valent (Prevenar 13, PCV13, Pfizer), as well as 23-valent polysaccharide vaccine (Pneumomax 23, Merk Sharp & Dohme). PCV13 is included in the national immunization schedule for vaccination of children.

Already early after the start of the national PCV13 vaccination program, a change in the serotype composition of the *S. pneumoniae* population among healthy children was observed, with the coverage of circulating serotypes by the PCV13 vaccine being about 50% [4]. Among the serotypes not covered by PCV13 vaccine, pneumococci of serogroups 15 and 11 predominate in vaccinated healthy children both in the early (2016-2018) [4] and late (2020–2022) periods after the start of vaccination [5–7]. It should be noted that serotypes 15BC and 11AD, which were not widespread in the pre-vaccination period, were found in children [8], as well as in adults [9, 10] with pneumococcal meningitis in the corresponding period [8].

In a pneumococcal population, there is often an association of a serotype with a particular genetic lineage - a group of closely related isolates belonging to one or more closely related clonal complexes (CC) or dominant sequencing types (ST). Populations of pneumococci of serogroups 15 and 11 have regional peculiarities. Thus, representatives of serogroup 15 are associated with genetic lineages CC-199 and CC-63 in the USA and Iceland, with CC-1025 and CC-1262 - in Russia (data from PubMLST database). Representatives of serogroup 11 are mainly associated with the ubiquitous genetic lineage CC-62, but the genetic lineage CC-1012 is also common in Russia. In some regions (Japan), an increase in the prevalence of multidrug-resistant strains of serotype 15A has been noted [11]. Thus, monitoring the antibiotic sensitivity of emerging epidemiologically significant genetic lineages is also important.

Due to the significant increase in the prevalence of serotypes of serogroups 15 and 11 among various population groups against the background of the widespread vaccination with PCV13, as well as due to their association with invasive diseases, the analysis of these strains is of fundamental and practical importance. In particular, identification of individual serotypes within these serogroups (since routine molecular typing methods do not allow differentiation of close serotypes), analysis of accumulated data on cross-immunogenicity of close serotypes, study of the invasive potential of genetic lineages associated with these serotypes — all this is important for determining the serotype composition of the future conjugated polysaccharide vaccine promising for Russia.

Objectives of the study — genetic analysis of *S. pneumoniae* serogroups 15 and 11 circulating in Russia according to the following parameters: serotype affiliation; clonal complex; presence of resistance and virulence determinants; relatedness to genetic lineages circulating in the world; presence of unique genes significant for virulence; justification of inclusion of the actual serotypes of serogroups 15 and 11 in the future conjugate vaccine composition.

Materials and methods

Sampling

The study included strains of serogroups 11 and 15 of *S. pneumoniae* from Russia for which full genomic data were available: isolates isolated at the Children's Research and Clinical Center for Infectious Diseases and the Botkin Clinical Infectious Diseases Hospital (St. Petersburg), Kazan Research Institute of Epidemiology and Microbiology (as part of the SAPIENS project). S.P. Botkin (St. Petersburg), Kazan Research Institute of Epidemiology and Microbiology (within the SAPIENS project), as well as full genomic data of isolates from different Russian cities obtained during the PEGAS study [10, 12].

The study was conducted with the voluntary informed consent of patients or their legal representatives. The study protocol was approved by the SAPIENS Ethical Committee (version 3.1 of 27.01.2020).

The choice of serotypes is explained by the significant spread of pneumococci belonging to these serotypes against the background of PCV13 vaccination, with only serotypes 11A and 15B included in the new PCV20 (Pfizer, currently not registered in Russia) and in Pneumomax 23. The selected isolates were isolated in different time periods (from 2001 to 2022) from carriers and patients with invasive diseases, from patients of different age groups. Two datasets were supplemented with full genomic data of *S. pneumoniae* strains isolated in different regions of the world — 23 strains for serogroup 11 dataset and 13 strains for serogroup 15 dataset. When selecting full-genomic data of *S. pneumoniae* from other regions of the world, the datasets included representatives of all available in the PubMLST database STs associated with the analyzed pneumococcal serotypes from different regions of the world with an interval of 1–4 years (depending on the prevalence).

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Serogroup 15 dataset included genomes of 45 isolates: 32 from Russia and 13 from other regions of the world. The analysis included whole genome data from isolates obtained from various clinical samples: patients with meningitis (n = 11; source of isolation — liquor), pneumonia (n = 11; source of isolation: 10 — sputum, 1 — not specified), acute otitis media (n = 3; source of isolation: middle ear fluid), carriers (n = 20; source of isolation — nasopharynx).

Serogroup 11 dataset included genomes of 38 isolates: 15 from Russia and 23 from other regions of the world. The analysis included whole genome data from isolates obtained from various clinical samples: patients with meningitis (n = 3; source of isolation — liquor), pneumonia (n = 8; source of isolation — sputum), acute otitis media (n = 3; source of isolation — middle ear fluid), carriers (n = 20; source of isolation — nasopharynx), in 1 case there was no information about the diagnosis (source of isolation – blood). For 3 isolates there was no information about the diagnosis and source of isolation.

Whole genome sequencing

Whole genome sequencing (WGS) of pneumococcal isolates isolated in St. Petersburg or within the SAPIENS project was performed at the Pasteur Research Institute of Epidemiology and Microbiology. DNA was isolated from pure cultures of *S. pneumoniae* using the QIAamp DNA Mini Kit (Qiagen). WGS was performed on the DNBSEQ-G50 platform (MGI). Libraries for WGS were prepared using the MGIEasy Fast FS DNA Library Prep Set (MGI) according to the manufacturer's standard protocols. The median length of library fragments was 430 bp (identified using the QIAxcel Advanced system capillary gel electrophoresis system). Sequencing to obtain paired-end reads was performed on the DNBSEQ-G50 platform (MGI) using DNBSEQ-G50RS kits (FCL PE150/FCS PE150). Whole genome data of 11 *S. pneumoniae* isolates uploaded to GenBank (BioProject PRJNA971376, BioProject PRJNA1009429, BioProject PRJNA1076328, BioProject PRJNA1154393).

Bioinformatics analysis

For isolates sequenced at the Pasteur Research Institute of Epidemiology and Microbiology, the quality of the obtained nucleotide sequences was assessed using the program FastQC v. 0.11.8 (Babraham Bioinformatics). Quality filtering of reads and removal of PCR adapters and primers used in library preparation were performed using the program Cutadapt v. 1.15. For *de novo* genome assembly, we used the algorithm SPAdes v. 3.15.4. Final quality assessment was performed using the Quast v. 5.0.2 program. ST determination by MLST typing (Multilocus sequence typing) was performed using the MLST v. 2.0 program[1]. Genomes were annotated using RAST server (Rapid Annotations using Subsystems Technology). The serogroup and serotype affiliation of the strains were determined using the blastall program with an E-value threshold < 0.01. The obtained matches were filtered by bit-score and identity values. Searches were performed against a locally customized *cps*-locus sequence database of 90 serotypes. Genes and mutations associated with antibiotic resistance were identified against the CARD database [13]. Methods for nuclear genome and pan-genome analysis (R package micropan: Microbial Pan-Genome Analysis v. 2.1) were used to compare genomes [14]. Clusters of orthologs were identified based on distances calculated by pairwise comparison of amino acid sequences. The clustering was based on the complete-linkage clustering method, in which the distance between clusters is equal to the maximum distance between points from different clusters, with threshold distance criterion being 0.75. To identify associations of unique clusters of orthologs with genetic lineages, the presence/absence/variability statistics of genes in the genomes of the analyzed isolates were estimated using the Scoary v. 1.6.16 package[2] [15].

Statistical analysis

For statistical processing we used the Scoary program, which allows us to obtain a list of genes significant for the corresponding trait, associated with the trait positively or negatively, sorted by p-values.

Results

To analyze the populations of *S. pneumoniae* serogroups 15 and 11 circulating in Russia and to characterize the genetic relationships between the genetic lines of serogroups 15 and 11 circulating in Russia and worldwide, pan-genome analysis was performed. For this purpose, two samples were formed, which included full genomic data of *S. pneumoniae* belonging to serogroups 15 and 11 from Russia and other regions of the world.

Analysis of S. pneumoniae serogroup 15

The study included full genomic data of 45 isolates of pneumococcus serogroup 15, including 32 isolates from different cities of Russia, as well as 13 isolates from other regions of the world (**Table 1**). Among the isolates of serogroup 15 isolated in Russia, 15 (46.9%) isolates belonged to serotype 15B, 12 (37.5%) to 15C, 3 (9.4%) to 15F, and 6 (6.3%) to 15A. Representatives of serotypes 15B/C were associated with 3 common STs (ST-1025, ST-199, ST-1262, of which only ST-199 is not found in Russia), as well as with rare STs. Serotypes 15A/F were associated predominantly with ST-63. ST-1025 isolates were isolated predominantly from sterile loci (isolation biomaterial — blood, liquor)

[1] Center for Genomic Epidemiology. URL: https://cge.food.dtu.dk/services/MLST/

[2] URL: https://github.com/AdmiralenOla/Scoary

Table 1. Characteristics of serogroup 15 strains

Sample	PubMLST ID / ENA_accession	Country	Region	Year of isolation	Serotype	ST	Patient's age, years	Diagnosis	Source of isolation	Penicillin	Erythromycin	Tetracycline	Chloramphenicol	Co-trimoxazole
PEGAS-5-1079	51104 [10, 12]	R	Yaroslavl	2016	15B	1025	11	MNG	CSF	S	S	S	S	R
PEGAS-5-1659	51117 [10, 12]	R	Yaroslavl	2017	15B	1262	2	MNG	CSF	S	S	S	S	S
PEGAS-2019-106	73021 [10, 12]	R	Yaroslavl	2019	15B	1262	1	MNG	CSF	S	S	S	S	S
PEGAS-2019-269	73025 [10, 12]	R	Yaroslavl	2019	15B	1025	0,2	MNG	CSF	S	S	S	S	R
PEGAS-2019-73	142552 [10, 12]	R	Yaroslavl	2019	15B	1025	78	PN	CSF	S	S	S	S	R
PEGAS-5-638	51109 [10, 12]	R	Smolensk	2016	15B	1025	50	MNG	CSF	S	S	S	S	R
PEGAS-2019-184	73023 [10, 12]	R	Smolensk	2019	15F	6202	52	MNG	CSF	S	S	S	S	S
PEGAS-2019-237	142578 [10, 12]	R	Smolensk	2019	15C	1025	63	PN	SP	S	S	S	S	R
PEGAS-2020-201	142624 [10, 12]	R	Yuzhno-Sakhalinsk	2020	15C	1025	23	PN	SP	S	S	S	S	R
PEGAS-2019-213	142574 [10, 12]	R	Yuzhno-Sakhalinsk	2019	15C	16380	2	PN	SP	R	S	S	S	R
PEGAS-2020-146	142613 [10, 12]	R	Kirov	2020	15C	1262	1	PN	SP	S	S	S	S	S
PEGAS-2019-343	142585 [10, 12]	R	Seversk	2019	15A	12518	55	PN	SP	S	S	S	S	S
PEGAS-2019-347	142587 [10, 12]	R	Seversk	2019	15C	16349	70	PN	SP	S	S	S	S	R
PEGAS-2019-373	142591 [10, 12]	R	Tomsk	2019	15C	1262	3	PN	SP	S	S	S	S	S
PEGAS-2019-375	142593 [10, 12]	R	Tomsk	2019	15B	1262	86	PN	SP	S	S	S	S	S
PEGAS-2019-390	142595 [10, 12]	R	Tomsk	2019	15C	1262	61	PN	SP	S	S	S	S	S
PEGAS-2020-229	142634 [10, 12]	R	Tolyatti	2020	15F	16421	45	PN	SP	S	S	S	S	S
ST_12518_2	ERR1788193	R	Moscow	2014	15A	12518	5	PHR	NPS	S	S	S	S	S
ST_3201_3	ERR1788219	R	Moscow	2015	15B	3201	2	–	NPS.	R	S	S	S	R
ST_1262_2	ERR1788207	R	Moscow	2013	15B	1262	5	–	NPS	S	S	S	S	R
ST_1262_3	ERR1788225	R	Moscow	2015	15B	1262	5	PHR	NPS	S	S	S	S	R
ST_1025_5	ERR1788208	R	Moscow	2014	15C	1025	5	PHR	NPS	S	S	S	S	R
ST_3557_1	ERR1788206	R	Moscow	2013	15B	3557	2	PHR	NPS	R	S	R	S	R

End of the Table 1

Sample	PubMLST ID / ENA_accession	Country	Region	Year of isolation	Serotype	ST	Patient's age, years	Diagnosis	Source of isolation	Penicillin	Erythromycin	Tetracycline	Chloramphenicol	Co-trimoxazole
6_2F1	PRJNA1154393	R	Moscow	2011	15F	6202		–	NPS	S	S	S	S	S
27_Kz	PRJNA971376	R	Kazan	2020	15C	1025	3	–	NPS	S	S	S	S	R
12001	PRJNA1076328	R	Saint-Petersburg	2016	15B	1262	3	–	NPS	S	S	S	S	S
12456	PRJNA1076328	R	Saint-Petersburg	2016	15B	1025	5	–	NPS	S	S	S	S	R
108	PRJNA1154393	R	Saint-Petersburg	2021	15C	1349		MNG	CSF	R	S	S	S	R
76_B	PRJNA1076328	R	Saint-Petersburg	2021	15B	1025	44	MNG	CSF	S	S	S	S	R
137_B	PRJNA1076328	R	Saint-Petersburg	2022	15C	1025	38	MNG	CSF	S	S	S	S	R
138_B	PRJNA1076328	R	Saint-Petersburg	2022	15C	1025	38	MNG	CSF	S	S	S	S	R
336_B	PRJNA1076328	R	Saint-Petersburg	2022	15B	Unkn_21	64	MNG	CSF	S	S	S	S	S
ST_63_3	ERR065297	U	Massachusetts	2004	15A	63	6	–	NPS	R	R	S	R	S
ST_63_4	ERR068032	U	Massachusetts	2004	15A	63	6	–	NPS	R	R	S	R	R
ST_63_5	ERR069724	U	Massachusetts	2004	15A	63	6	–	NPS	R	R	S	R	S
ST_199_1	ERR069751	U	Massachusetts	2001	15C	199	2	–	NPS	S	S	S	S	S
ST_199_2	ERR069691	U	Massachusetts	2004	15B	199	2	–	NPS	S	S	S	S	S
ST_199_3	ERR069774	U	Massachusetts	2001	15C	199	2	–	NPS	S	S	S	S	S
ST_199_4	ERR065975	U	Massachusetts	2001	15B	199	2	–	NPS	S	S	S	S	S
ST_199_11	ERR540653	I	Reykjavik	2010	15B	199	2	–	NPS	S	S	S	S	S
ST_199_16	ERR755466	I	Reykjavik	2013	15C	199	2	OM	MEF	S	S	S	S	S
ST_199_17	ERR755326	I	Reykjavik	2013	15B	199	3	OM	MEF	S	S	S	S	S
ST_199_13	ERR470151	I	Koupavogur	2009	15C	199	4	–	NPS	S	S	S	S	S
ST_199_18	ERR755336	I	Habnarfjordur	2013	15B	199	2	OM	MEF	S	S	S	S	S
ST_199_21	ERR755384	I	Habnarfjordur	2014	15C	199	4	–	NPS	S	S	S	S	S

Note. MNG — meningitis; PN — pneumonia; Phr — pharyngitis; OM — otitis media; CSF — cerebrospinal fluid; SP — sputum; NPS — nasopharyngeal smear; MEF — middle ear fluid; R/S — presence/absence of determinants of resistance (source: Prediction of antimicrobial resistance in PATRIC and RAST, URL: https://www.bv-brc.org/job).

and more frequently were associated with invasive diseases. Most isolates of this serogroup 15 were sensitive to antibiotics of different classes. Detailed characteristics of the analyzed isolates (ST, source of isolation, year of isolation, presence of antibiotic resistance determinants in the genomes, etc.) are presented in **Table 1**.

The pan-genome of *S. pneumoniae* isolates of serogroup 15 was characterized by comparing all proteins (blast-all-all). In representatives of serogroup 15 the share of the main (conserved) part of the genome was 59.8% — 1286 genes were present in all genomes of the analyzed sample (**Fig. 1**). In the population of serogroup 15, 2097 clusters of orthologs were identified, the most numerous cluster was represented by 296 proteins. The pan-genome of pneumococcus serogroup 15 isolates belongs to the closed pan-genome (alpha index value > 1), and its size approaches a constant as more genomes are used (Hipps' law) [14]. This may indicate that the genome diversity of serogroup 15 representatives has reached saturation, regardless of the time period and geographic region of isolates isolation, as well as their belonging to the genetic lineage.

All representatives of the genetic lineage ST-1025 are associated with a homogeneous dendrogram cluster describing the relationship between strains based on pan-genome analysis and taking into account both the presence or absence and homology of available amino acid sequences (**Fig. 2**). All ST-1025 representatives contain in their genomes a unique operon encoding oligopeptide transporter components. Furthermore, ST-1025 representatives contain in their genomes a unique operon encoding components of the fructose-specific phosphotransferase transport system (PTS). ST-1025

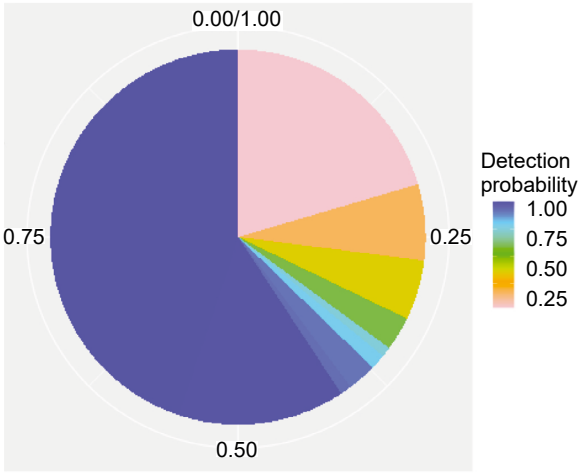

Fig. 1. Distribution of gene families of the pan-genome of *S. pneumoniae* serogroup 15 strains.
The color of the sector reflects the probability of identification of the gene family in the genomes of isolates. The blue color shows highly conservative («core genome») gene families.

isolates also contain unique variants of hydrolases, iron ion transporters, and the zinc metalloprotease gene *ZmpC* (**Table 2**).

Along with ST-1025, the prevalence of ST-1262 may be associated with the presence in the genomes of its representatives of factors that provide higher adaptability to stress conditions (**Table 3**).

Analysis of S. pneumoniae serogroup 11

The sample of serogroup 11 representatives included full genomic data of 15 isolates from different cities of Russia, as well as 23 isolates from other re-

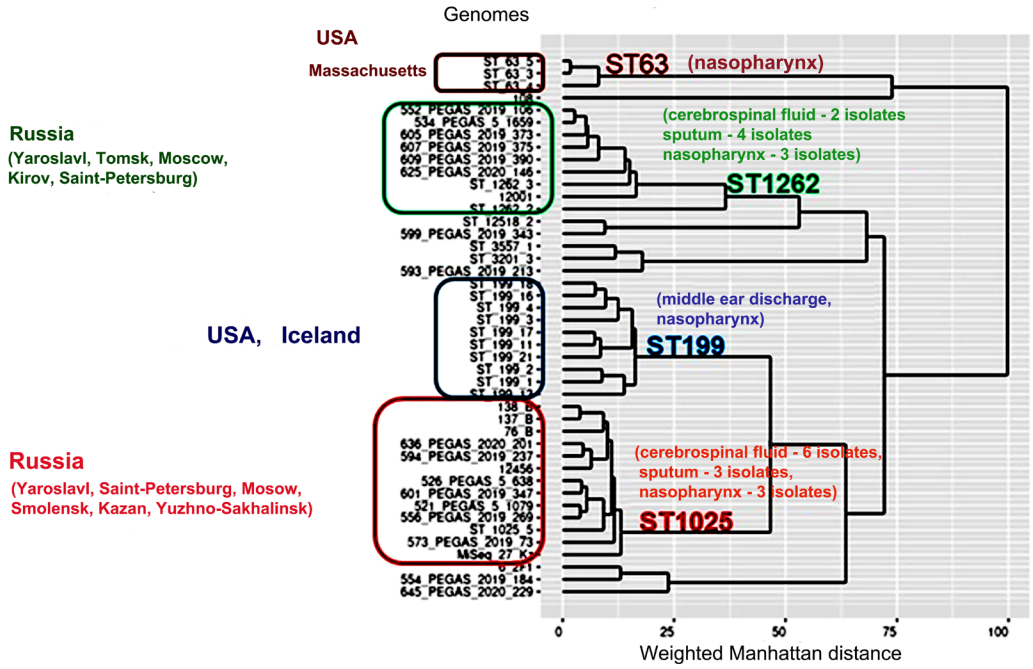

Fig. 2. A dendrogram describing the clustering of *S. pneumoniae* isolates of serogroup 15 by pan-genome R micropan analysis (presence/absence and gene homology).

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Table 2. Unique proteins of the CC-1025 genetic lineage representatives*

Sequence ID	Homology with known proteins, %	Protein name	Proposed function
27_Kz_seq27	100	ABC iron (III) transporter, permease	Transport of iron III+ ions
27_Kz_seq161	96	ABC transporter, permease	Transport of iron III+ ions
27_Kz_seq266	97,9	Membrane succinate permease DctA, sodium symporter	Transport of dicarboxylic acids
27_Kz_seq792	100	Component IIC of the phosphotransferase system (PTS)	Protein-N(PI)-phosphohistidine-fructose-PTS
27_Kz_seq793	99	Component IIB of the PTS	
27_Kz_seq794	100	Component IIA of the PTS	
27_Kz_seq795	100	Hypothetical nitrogen regulatory protein IIA of the PTS system	
27_Kz_seq796	99,9	A hypothetical transcription antiterminator of the BglG family	
27_Kz_seq1007	100	High affinity permease Fe^{2+}/Pb^{2+}	Ferrum ions transport
27_Kz_seq1008	99,7	DyP-type peroxidase (IPR006314)	DyP proteins have characteristics that distinguish them from other peroxidases: broad substrate specificity, lack of homology with most other peroxidases, and the ability to function well under conditions of lower pH values
27_Kz_seq1359	99,9	Zinc-dependent metalloproteinase ZmpC	Cleaves and activates human matrix metalloproteinase-9. The role in the virulence and pathogenicity of pneumococcus in the lungs
27_Kz_seq1361	100	Hypothetical acetyltransferase	Unknown
27_Kz_seq1489	100	N-acetylneuramic acid epimerase	Mutarotation of sialic acids. The presence of sialic acids in the elements of the bacterial cell surface helps them evade the innate immune response of the host
27_Kz_seq1490	100	Substrate-binding subunit AppA, ABC component of the oligopeptide transporter	Transport of oligopeptides
27_Kz_seq1494	99,8	Hypothetical glycosylhydrolase family 32	Unknown

Note. *These proteins are encoded in the genomes of 13 isolates: 556_PEGAS_2019_269, 573_PEGAS_2019_73, 594_PEGAS_2019_237, 601_PEGAS_2019_347, 636_PEGAS_2020_201, 76_B, MiSeq_27_Kz, ST_1025_5, 12456, 137_B, 138_B, 521_PEGAS_5_1079, 526_PEGAS_5_638)

gions of the world. Among the isolates of serogroup 11 isolated in Russia, 13 (86.7%) isolates belonged to serotype 11A and 2 (13.3%) to serotype 11D. Representatives of serogroup 11 were associated with two common genetic lineages: CC-62 (circulating ubiquitously) and CC-1012, as well as with rare STs. Isolates belonging to CC-62 were isolated predominantly from the nasopharynx. Isolates belonging to CC-1012 were frequently associated with invasive diseases (biomaterial of isolation was liquor). Most isolates of serogroup 11 were sensitive to antibiotics of different classes (**Table 4**).

Pan-genome analysis of *S. pneumoniae* isolates of serogroup 11 showed a higher degree of genome heterogeneity in this group (**Fig. 3**). The share of the main (conserved) part of the genome was 36% — 820 genes were present in all genomes of the analyzed sample (**Fig. 3**). In the population of serogroup 11, 1864 clusters of orthologs were identified, the most numerous cluster was represented by 191 proteins. The pan-ge-

Table 3. Unique proteins of the CC-1262 genetic lineage representatives*

Sequence ID	Homology with known proteins, %	Protein name	Proposed function
552_PEGAS_2019_106_seq440	100	Phage shock protein PspC	The integrity of the inner membrane in response to extracytoplasmic stress conditions
552_PEGAS_2019_106_seq590	100	Satellite phage hypothetical protein (*Streptococcus satellite phage Javan725*)	Prophage component
552_PEGAS_2019_106_seq591	100	Satellite phage hypothetical protein (*Streptococcus satellite phage Javan296*)	Prophage component
552_PEGAS_2019_106_seq592	100	Primase C-terminal 1 domain-containing protein	Prophage component
552_PEGAS_2019_106_seq624	100	Methionine tRNA ligase	The initiation of protein synthesis
552_PEGAS_2019_106_seq686	98,6	ABC transporter, ATP-binding subunit, GlnQ	Transport of glutamine
552_PEGAS_2019_106_seq915	99	Superfamily 2 helicase	Unknown
552_PEGAS_2019_106_seq1038	99,4	O-acetylhomoserine aminocarboxypropyltransferase	Synthesis of methionine
552_PEGAS_2019_106_seq1080	91	AAA ATPase	ATP hydrolysis
552_PEGAS_2019_106_seq1081	85	Serine protease	Possible signaling function
552_PEGAS_2019_106_seq1112	100	Hypothetical macrolide efflux transporter	Possible macrolide efflux
552_PEGAS_2019_106_seq1113	100	Hypothetical protein	Unknown
552_PEGAS_2019_106_seq1114	100	Group I pyridoxal-dependent decarboxylase (cleaves Orn/Lys/Arg and glycine)	Amino acid metabolism

Note. *These proteins are encoded in the genomes of 10 isolates: PEGAS_2019_106, 605_PEGAS_2019_373, 607_PEGAS_2019_375, 609_PEGAS_2019_390, 12001, 625_PEGAS_2020_146, ST_1262_2, ST_1262_3, 534_PEGAS_5_1659, 552_PEGAS_2019_106

nome of the pneumococcal isolates of serogroup 11 serogroup 11 belonged to the open pan-genome — the alpha index value < 1 (0.82), i.e. the pan-genome size of this group should increase, as more genomes are included in analysis. This may indicate greater variability of genomes of this group and greater diversity of the additional part of the genome of representatives of serogroup 11 (**Fig. 4**), their potentially greater adaptability. This fact is consistent with the high prevalence of CC-62 in different regions of the world in different periods of time.

SS-62 representatives contain in their genomes a unique operon encoding the synthesis of bacteriocin involved in interspecific competition, oligopeptide transporter components, and flavin reductase-like protein that promotes adhesion and protects the bacterium from oxidative stress, which increases the virulence of the microorganism (**Table 5**). Also, all representatives of SS-62 contain a fucose processing operon and PsaA

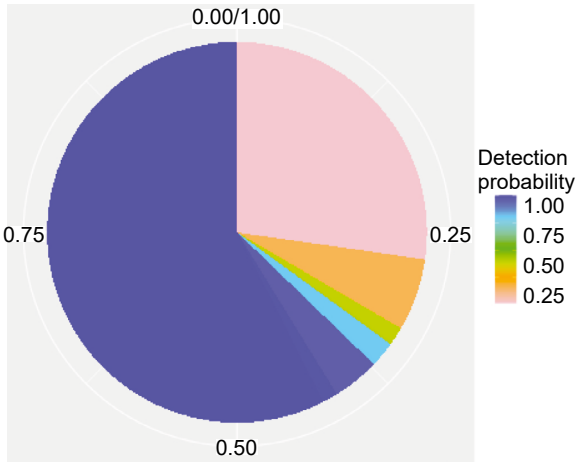

Fig. 3. Distribution of gene families of the pan-genome of *S. pneumoniae* serogroup 11 strains.

The color of the sector reflects the probability of identification of the gene family in the genomes of isolates. The blue color shows highly conservative («core genome») gene families.

Table 4. Characteristics of serogroup 11 strains

Sample	PubMLST / ENA_accession number	Country	Region	Isolation year	Serotype	ST	Patient's age, years	Diagnosis	Source of isolation	Penicillin	Erythromycin	Tetracycline	Chloramphenicol	Co-trimoxazole
PEGAS-2019-401	73030 [10, 12]	Russia	Krasnodar	2019	11A	1012	61	MNG	CSF	S	S	S	S	S
PEGAS-2019-64	142555 [10, 12]	Russia	Yaroslavl	2019	11A	156	66	PN	SP	S	S	R	R	R
PEGAS-2019-113	142568 [10, 12]	Russia	Smolensk	2019	11A	1012	57	PN	SP	S	S	S	S	S
PEGAS-2019-344	142586 [10, 12]	Russia	Seversk	2019	11D	62	67	PN	SP	S	S	S	S	S
PEGAS-2019-349	142588 [10, 12]	Russia	Seversk	2019	11A	1012	85	PN	SP	S	S	S	S	S
PEGAS-2020-149	142616 [10, 12]	Russia	Kirov	2020	11A	6191	62	PN	SP	S	S	S	S	R
PEGAS-2020-150	142617 [10, 12]	Russia	Kirov	2020	11A	62	1	PN	SP	S	S	S	S	S
PEGAS-2020-226	142631 [10, 12]	Russia	Tolyatti	2020	11A	62	34	PN	SP	S	S	S	S	S
PEGAS-2019-114	142560 [10, 12]	Russia	Moscow	2019	11A	1012	72	PN	SP	S	S	S	S	S
ST_62_27	ERR1788222	Russia	Moscow	2012	11A	62	5	–	NPS	S	S	S	S	S
ST_62_28	ERR1788215	Russia	Moscow	2014	11A	62	5	PhR	NPS	S	S	S	S	S
ST_1012_3	ERR1788171	Russia	Moscow	2013	11A	1012	3	MNG	CSF	S	S	S	S	S
ST_1012_4	ERR1788140	Russia	Moscow	2011	11A	1012	3	MNG	CSF	S	S	S	S	S
105_Kz	PRJNA1009429	Russia	Kazan	2020	11D	62	4	–	NPS	S	S	S	S	S
25_B	PRJNA1076328	Russia	Saint Petersburg	2021	11A	1050	60	–	BL	S	S	S	S	S
ST_62_3	ERR069801	USA	Massachusetts	2001	11A	62	2	–	NPS	S	S	S	S	S
ST_62_4	ERR069822	USA	Massachusetts	2001	11A	62	3	—	NPS	S	S	S	S	S
ST_62_5	ERR065964	USA	Massachusetts	2001	11A	62	3	—	NPS	S	S	S	S	S
ST_62_6	ERR069804	USA	Massachusetts	2001	11A	62	6	–	NPS	S	S	S	S	S
ST_62_7	ERR065326	USA	Massachusetts	2004	11A	62	2	—	NPS	S	S	S	S	S
ST_62_8	ERR069707	USA	Massachusetts	2004	11A	62	2	–	NPS	S	S	S	S	S
ST_62_9	ERR069727	USA	Massachusetts	2004	11A	62	2	–	NPS	S	S	S	S	S
ST_62_10	ERR065310	USA	Massachusetts	2004	11A	62		–	NPS	S	S	S	S	S

End of the Table 4

Sample	PubMLST / ENA_accession number	Country	Region	Isolation year	Serotype	ST	Patient's age, years	Diagnosis	Source of isolation	Penicillin	Erythromycin	Tetracycline	Chloramphenicol	Co-trimoxazole
ST_62_11	ERR124268	USA	Massachusetts	2007	11A	62	6	–	NPS	S	S	S	S	S
ST_62_12	ERR129079	USA	Massachusetts	2007	11A	62	6	–	NPS	S	S	S	S	S
ST_62_13	ERR129211	USA	Massachusetts	2007	11A	62	6	–	NPS	S	S	S	S	S
ST_62_14	ERR129131	USA	Massachusetts	2007	11A	62	6	–	NPS	S	S	S	S	S
ST_62_15	ERR470324	Iceland	Reykjavik	2009	11A	62	3	–	NPS	S	S	S	S	S
ST_62_16	ERR449847	Iceland	Reykjavik	2009	11A	62	65	PN	NA	S	S	NA	NA	NA
ST_62_20	ERR470201	Iceland	Reykjavik	2010	11A	62	11	OM	MEF	S	S	S	S	S
ST_62_21	ERR540645	Iceland	Reykjavik	2010	11A	62	5	–	NPS	S	S	S	S	S
ST_62_22	ERR540483	Iceland	Reykjavik	2010	11A	62	60	PN	NA	S	S	S	S	S
ST_62_17	ERR470261	Iceland	Mosfellsbaer	2009	11A	62	17	OM	MEF	S	S	S	S	S
ST_62_18	ERR449827	Iceland	Mosfellsbaer	2009	11A	62	42	PN	NA	S	S	S	S	S
ST_62_19	ERR470192	Iceland	Selfoss	2010	11A	62	1	OM	MEF	S	S	S	S	S
ST_62_23	ERR755493	Iceland	Hafnarfjörður	2014	11A	62	5	–	NPS	S	S	S	S	S
ST_62_24	ERR755501	Iceland	Hafnarfjörður	2014	11A	62	5	–	NPS	S	S	S	S	S
ST_62_26	ERR755548	Iceland	Kopavogur	2014	11A	62	6	–	NPS	S	S	S	S	S

Note. MNG — meningitis; PN — pneumonia; Phr — pharyngitis; OM — otitis media; CSF — cerebrospinal fluid; SP — sputum; NPS — nasopharyngeal smear; MEF — middle ear fluid; R/S — presence/absence of determinants of resistance (source: Prediction of antimicrobial resistance in PATRIC and RAST. URL: https://www.bv-brc.org/job).

(a component of the ATP-binding cassette transporter that imports manganese ions and is also an adhesin).

Representatives of the SS-1012 genetic lineage are less common, also mostly associated with serotype 11A, but isolated mainly from liquor and sputum. The unique features of this genetic lineage include the presence of the Streptococcus satellite phage Javan359. Representatives of SS-1012 have a bacteriocin unique to this genetic lineage. Also, SS-1012 isolates may have peculiarities of amino acid synthesis and riboflavin biosynthesis, which may be related to virulence, but this assumption needs to be verified in additional studies.

Discussion

Since the introduction of PCV-13 into national immunization schedules, reports of increased circulation of *S. pneumoniae* serogroup 15, which is not covered by PCV13, have begun to appear [16–18]. 15B is one of the serotypes currently associated with relatively high mortality rates [19–22], development of invasive forms, particularly meningitis [23, 24]. According to recent-

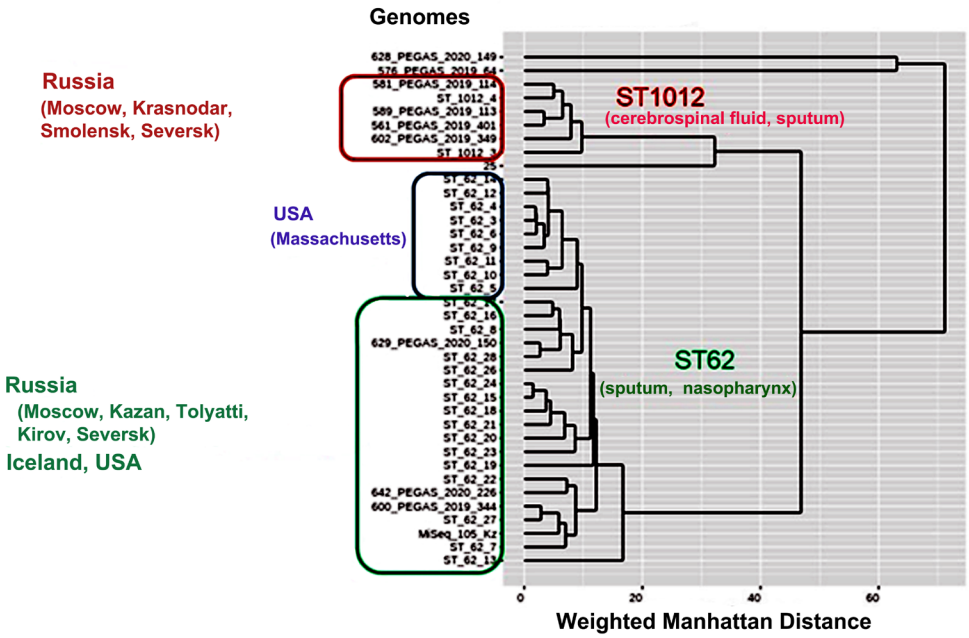

Fig. 4. Dendrogram describing the clustering of *S. pneumoniae* serogroup 11 isolates by pan-genome R micropan analysis (presence/absence and gene homology).

ly published results of Chinese researchers, the most common circulating among children in China is pneumococcal serogroup 15 [25]. In Russia there is also a tendency of expansion of this serogroup [5, 6]. According to the results of our analysis, the two most common genetic lineages of serogroup 15 circulating in Russia, CC-1025 and CC-1262, are often associated with invasive diseases. Isolates of CC-1025 and CC-1262 are represented by serotypes 15B/C and have genetic determinants that may contribute to better adaptation and success of these genetic lineages and may potentially be associated with virulence (**Tables 2, 3**). In particular, oligopeptide transporters, in addition to transporting bacteriocins and chemokines, may be associated with the regulation of the expression of choline-binding proteins [26, 27]. A unique variant of fructose-specific PTS may also contribute to the selection of ST-1025 representatives in carriers on the background of vaccination due to energetic advantages. The zinc metalloprotease ZmpC specifically cleaves and activates human matrix metalloproteinase-9, which in turn degrades components of the extracellular matrix [28]. All ST-1262 strains contain a gene encoding a peptide that accounts for resistance to abortive phage infection (**Table 3**). As part of the satellite prophage, all representatives of ST-1262 have a gene encoding a phage shock protein that ensures the integrity of the cell inner membrane in response to extracytoplasmic stress conditions. It is possible that ST-1262 representatives have peculiarities of amino acid metabolism (**Table 3**), but this assumption needs to be verified.

Thus, potentially virulent pneumococci of serotypes 15B and 15C are circulating in Russia. It was previously established that the structural difference between these serotypes is based on variations in the short tandem repeat of thymine-adenine nucleotides in the *wciZ* O-acetyltransferase gene, which ensure mutual switching of serotypes 15B and 15C [29, 30]. The cross-immunogenicity of serotypes 15B/C with the formation of stable antibody titers was confirmed in earlier studies [30, 31]. Thus, vaccines containing serotype 15B could potentially limit the spread of virulent genetic lineages associated with serotypes 15B/C in the pneumococcal population.

According to the results of various studies, serotype 11A is currently spreading worldwide [32], both in pneumococcal carriers [33] and in invasive diseases [34]. According to A.B. Brueggemann et al, serotype 11A is more associated with asymptomatic carriers than with invasive disease, indicating a relatively low virulence potential [35]. However, some ST-62 strains of serotype 11A are capable of causing invasive diseases with high lethality [36]. According to the results of our study, ST-62 representatives contain in their genomes loci potentially capable of increasing the adaptability and virulence of the microorganism: loci encoding the synthesis of bacteriocins, transporters, including oligopeptides, adhesion proteins, flavin reductase, oxidative stress defense factors, complement activation regulators, and transcription regulators (**Table 5**). Our results are confirmed by the data of previous studies [37]. Thus, the research group of M.A. Higgins et al. previously showed the inability of *S. pneumoniae* to grow on fucose, despite the presence of regulatory and biochemical mechanisms of fucose metabolism [38]. It is assumed that the fucose processing pathway of

Table 5. Unique proteins of the serogroup 11 genetic lineages representatives

ID последовательности Sequence ID	Homology with known proteins, %	Protein name	Proposed function
		CC-62* — 29 isolates	
GID11_seq178	100	Bacteriocin	Interspecific competition
GID11_seq180	87,5	Transposase ISSmu1	Prophage component
GID11_seq303	98,8	O6-methylguanine DNA methyltransferase	DNA repair. Maintaining the stability of the genome
GID11_seq357	100	L-fuculose phosphate aldolase	Metabolism of fucose
GID11_seq358	99,3	RbsD/FucU family transport protein	
GID11_seq359	98,6	Enzyme IIA component of the phosphotransferase system (PTS)	
GID11_seq363	99,6	Hypothetical protein	Unknown
GID11_seq364	99,8	F5/8 type C domain-containing protein	It can act as a protective agent. Possibly, regulation of complement activation (lectin pathway)
GID11_seq373	56	Pneumococcal surface protein A-like protein	An adhesive and a component of an ATP-binding cassette conveyor importing manganese ions. It is possible that PsaA, like many other virulence factors, performs two functions during infection: direct adhesion and participation in the absorption of manganese
GID11_seq740	97,7	Hypothetical helicase	Unknown
GID11_seq974	51,8	ABC transporter, permease	Transport
GID11_seq975	52,7	ABC transporter, ATP-binding subunit	
GID11_seq976	43,3	ArsR family transcriptional regulator	
GID11_seq1078	96,9	Superfamily II group DNA or RNA helicases	Possible regulation of expression
GID11_seq1083	100	Flavin reductase-like domain-containing protein	Flavin reductase is present on the surface of pneumococci. It promotes virulence by protecting against oxidative stress and mediating adhesion
GID11_seq1103	95,5	Transcription regulator BlpS	The domain binding to DNA
GID11_seq1185	28,8	Component of the antimicrobial peptides ABC transport system	Interspecific competition
GID11_seq1585	28	HECT domain containing protein	Ubiquitin-protein ligases — protein utilization
		CC-1012 — 6 isolates**	
GID12_seq99	100	Guanosine triphosphate cyclohydrolase	The opening of the imidazole ring of guanosine triphosphate is catalyzed. An obligatory stage of biosynthesis of a variety of coenzymes (riboflavin and folate), tRNA bases
GID12_seq198	100	Hypothetical macrolide efflux protein	Possible macrolide efflux

End of the Table 5

ID последовательности Sequence ID	Homology with known proteins, %	Protein name	Proposed function
GID12_seq199	99,8	Hypothetical protein	Unknown
GID12_seq200	100	Group I pyridoxal-dependent decarboxylase (cleaves Orn/Lys/Arg and glycine)	Amino acid metabolism
GID12_seq887	98,3	Competence system transport protein	Natural competence system
GID12_seq1238	87,9	DNA-binding protein of the satellite phage *Streptococcus satellite phage Javan359*	Prophage component
GID12_seq1240	100	Hypothetical satellite prophage protein *Streptococcus satellite phage Javan735*	Prophage component
GID12_seq1279	91,4	Argininosuccinate synthetase, rgG	Amino acid biosynthesis; L-arginine biosynthesis (L-arginine from L-ornithine and carbamoyl phosphate
GID12_seq1281	98,4	Bacteriocin-like peptide	

Note. *The ST62 group: 642_PEGAS_2020_226, MiSeq_105_Kz, ST_62_10, ST_62_11, ST_62_12, ST_62_13, ST_62_14, ST_62_15, ST_62_16, ST_62_17, ST_62_18, ST_62_19, ST_62_20, ST_62_21, ST_62_22, ST_62_23, ST_62_24, ST_62_26, ST_62_27, ST_62_28, ST_62_3, ST_62_4, ST_62_5, ST_62_6, ST_62_7, ST_62_8, ST_62_9, 600_PEGAS_2019_344, 629_PEGAS_2020_150.
**The ST1012 group: ST_1012_3, ST_1012_4, 561_PEGAS_2019_401, 581_PEGAS_2019_114, 589_PEGAS_2019_113, 602_PEGAS_2019_349.

S. pneumoniae plays a non-metabolic role in the interaction of this bacterium with the human host. Pneumococcal surface adhesin A (PspA) prevents activation of both classical and alternative complement pathways through its interaction with the C3b component [39]. PspA also interacts with human lactoferrin, inhibiting its bactericidal action [39]. Flavin reductase is present on the surface of pneumococci and promotes virulence by protecting against oxidative stress and mediating adhesion, and provides protection against pneumococcal infection [40]. The immune response to this protein increases with age [40]. SS-62 representatives contain other hypothetical regulators of complement activation, ABC-transporters and transcription regulators. Probably, the presence of a large number of adaptive factors allowed the genetic lineage ST-62, associated mainly with serotype 11A, to spread widely throughout the world.

Serogroup 11 includes 6 antigenically different serotypes (11A-11F) with highly homologous *cps* loci. The structural difference between the serotypes is due to either the mutations in the *wcjE* gene (manifested in serotypes 11A and 11E by differences in the degree of β-galactose-6-O-acylation) [41], or the N112S mutation in the *wcrL* glycosyltransferase gene (manifested by the addition of an additional carbohydrate residue to the repeating unit of the carbohydrate chain of the capsule in serotype 11D) [42]. Studies have shown that vaccines containing serotype 11A are very likely to limit the spread of serotype 11E, but not serotypes 11B, 11C, 11F, nor 11D (due to the presence of 2 types of carbohydrate chain structural units in its capsule) [43]. However, all serotypes except 11A are not widely distributed, and their inclusion in a future vaccine is not yet necessary.

There is no doubt that specific prophylaxis with pneumococcal vaccines plays a huge role in reducing invasive forms of pneumococcal infections both among children and adults, as evidenced by numerous publications from various countries that have introduced this vaccination into national calendars. However, the undeniable fact is the increased prevalence of non-vaccine serotypes of pneumococci, the invasive potential of which still requires clarification and additional research. One of the ways to further improve specific prophylaxis, some authors suggest the development of new vaccines with high valence. But it should also be taken into account that structural similarity between capsular polysaccharides of closely related serotypes of pneumococci may lead to induction of cross-reacting antibodies against serotype not covered by PCV, which may provide additional protective clinical effect.

Conclusion

Vaccination against invasive variants of pneumococci has played an important role in the spread of non-vaccine serotypes, and the epidemic processes associated with their expansion are a consequence and evidence of the effectiveness of vaccination. Serotype-specific vaccination leads to the spread of serotypes not covered by vaccines, some of which may exhibit increased virulence and/or antimicrobial resis-

tance. In Russia, serogroups 15 and 11 are common among non-vaccine serogroups. No antimicrobial resistance determinants have been identified in the genomes of representatives of these serogroups. For each of the genetic lineages associated with serogroups 15 and 11 common in Russia, virulence determinants unique within the serogroup under study have been identified, which may contribute to the success of these lineages. Given the high virulence potential and prevalence, we can predict an increase in the epidemiologic importance of these genetic lineages in Russia. Inclusion of serotypes 15B and 11A in vaccines for use in Russia is advisable.

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