

The pathogenicity of the *Streptococcus* genus

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Abstract *Streptococcus* infections are still one of the important problems facing contemporary medicine. As the World Health Organization (WHO) warns, *Streptococcus pneumoniae* is responsible for the highest number of pneumonia cases all over the world. Despite an increasing number of pneumococcal vaccinations, incidences of disease connected to this pathogen's infection stay at the same level, which is related to a constantly increasing number of infections caused by nonvaccinal serotypes. Unfortunately, the pathogenicity of bacteria of the *Streptococcus* genus is also connected to species considered to be physiological flora in humans or animals and, additionally, new species exhibiting pathogenic potential have been discovered. This paper presents an opinion concerning the epidemiology of streptococci infections based on case studies and other publications devoted to this problem. It also sheds new light based on recent reports on the prevention of protective vaccinations application in the case of streptococci infections.

Selected factors of the pathogenicity of streptococci described in this paper

The term *pathogenicity determinant* refers to those features which determine the ability of a microorganism to cause a disease, but which are not themselves required for its survival [1]. Henderson et al. define pathogenicity determinants as pathogen components which cause damage in a host organism; this may include factors which are important for

pathogen survival [2]. These definitions, however, do not take into account the role of host susceptibility to infection; instead, they note only those features of the pathogen which are responsible for disease development. According to these definitions, only those organisms which cause diseases in healthy people are pathogens, while opportunistic or commensal microorganisms, which are only able to infect hosts with immune system disorders, are not considered to be pathogens.

Casadevall and Pirofski [3] proposed a new definition of pathogenicity and pathogenicity determinants for microorganisms which encompassed the state of a host's immunological defenses. The pathogenicity of a given microorganism was expressed as the degree of damage caused both by the microorganism itself and by the immune system in response to the pathogen.

One of the most invasive groups of bacteria is the *Streptococcus* genus. It is divided into 49 species and eight subspecies, from which as many as 35 have been identified as sources of invasive infections in humans. Microorganisms considered to be the cause of common infections include: *S. pneumoniae*, *S. pyogenes*—group A (group A *Streptococcus*, GAS), *S. agalactiae*—group B (group B *Streptococcus*, GBS), and *S. mutans* [4].

According to the estimations of the World Health Organization (WHO), about 1.2 million children aged below 5-years die each year as a result of pneumonia, for which the main casual factor is *S. pneumoniae*, and this constitutes 18 % of all deaths in this age group [5]. The high incidence of the above diseases and the mortality related to *S. pneumoniae* infections have prompted scientists to seek to develop vaccines aimed at reducing the incidence of such infections. It is known that the main factor underlying microorganism pathogenicity is the so-called polysaccharide envelope [6], which was the basis of the division of the *S. pneumoniae* microorganism into over 90 serotypes [7–9]. Seventeen immunogenic proteins have been identified on

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this microorganism surface, and the occurrence of 13 of them is dependent on the host age [4]. Polysaccharide antigens are used in anti-pneumococcal vaccines. They are conjugated in the vaccines with proteins in order to enhance the immunological response, i.e., with respect to that which would occur during natural infection by bacteria within the polysaccharide envelope [10]. Conjugation of these substances allows successful immunization of children before the second year of life, who are, at this age, a reservoir of numerous opportunistic pathogenic bacteria [8].

S. pneumoniae is characterized by significant genetic flexibility and, thus, is subject to natural transformations which allow it to obtain new phenotypic features. Recombinations occurring in this manner within the polysaccharide envelope enable the microorganism to circumvent the barrier formed by the host's immune system [4]. Therefore, numerous types of vaccines against *S. pneumoniae* have been created so far, and further research on bacterial strains has formed the basis for widening the list of antigens which may constitute a potential target for the activity of future generations of vaccines.

The next most common cause of diseases and mortality worldwide are invasive GAS infections. *S. pyogenes* are responsible for about 700 million infections per year, which result in the death of about 500,000 people [11]. One of the most common *S. pyogenes* strains is the strain M1T1, which is responsible for both pharyngitis and more severe conditions, such as necrotizing fasciitis or toxic shock syndrome. This bacteria is equipped with flagella referred to as antigen T. However, unlike the flagella observed in *S. pneumoniae*, the presence of the flagella in *S. pyogenes* causes decreased invasiveness and pathogenicity of the strain. Despite the similarity of both kinds of flagella in general, i.e., the main genetic structure, fine differences in particular genes enable functional diversity between the encoded proteins. The flagella of the M1T1 strain increase the adhesive abilities of the proteins towards the endothelium; however, they concurrently constitute a molecular pattern for phagocytary cells of the host, and, thus, are subject to higher activity and faster elimination from an organism [12].

During a study conducted on *S. pyogenes*, 66 new proteins related to the cell membrane were identified for the first time on the surface of this microorganism, and as many as half of them are immunoreactive proteins and 23 are exposed on the cell surface [4]. Such huge differentiation of surface proteins enables wide-ranging research to be conducted on vaccines, the target of whose activity would be various kinds of antigens. One of the main factors of *S. pyogenes* pathogenicity is streptococcal pyrogenic exotoxin B (SpeB) of an activity of cysteine protease [4]. SpeB is formed by most GAS strains, and, therefore, any decrease in virulence may also be affected by an inhibition of *speB* gene expression or by the chemical inactivation of the protein itself. Other factors affecting GAS virulence also include: streptolysin O, protein M, SpeA, or

streptokinase, which are also targets of therapeutic activity during infections. Despite extensive studies on GAS, no licensed vaccine against this group of microorganisms has been created so far [11]. This is influenced, inter alia, by the large serotypic differentiation of protein M, which was considered at the beginning of the 21st century to offer the potential for vaccine applications [4, 11]. A 6-valent vaccine against GAS containing N-end parts of six serotypes of protein M and tested on animals gave a desirable effect—an increase in the level of antibodies directed towards antigens contained within it. In the first stage of clinical trials, an increase in the number of antibodies was also demonstrated, and, additionally, no cross-reactions with human tissues were reported. The vaccine is the subject of further tests; however, a disadvantage attributed to it is its defense against only 6 of the 120 suggested serotypes of protein M [4]. The development of genetic research conducted on *S. pyogenes* may, in the future, allow an elaboration of methods which would identify antigens suitable for application in vaccines. Such research was performed in silico by Sharma et al. [11]. It resulted in the identification of the genes for 309 surface proteins, among which 260 present in at least 6 of the 8 examined strains were selected. Next, 147 proteins were selected for which it was possible to establish a topology on the microorganism cell surface, and their origin was determined. It appeared that many of these proteins are factors of *S. pyogenes* virulence. After an analysis of 81 of the 147 genes, it was demonstrated that 82 % of them are present in all the examined GAS isolates, while 73 of them (90.12 %) occur in over 80 % of the isolates. As a result, 52 proteins which may constitute the target of future vaccines were presented. Genetic research is accelerating the creation of a vaccine against GAS, since it considerably widens the list of surface antigens which may be used. Additionally, they confirm the occurrence of particular proteins on numerous bacterial strains, which may lead to successful worldwide application of vaccinations. The research also established that serotype M1 is less invasive compared to serotype M49; however, this requires confirmation via additional research [11].

GBS, *S. agalactiae*, has become an equally important microorganism which is responsible for miscarriages, and may also constitute a risk of premature birth and neonate infection in the form of sepsis, pneumonia, or meningitis. In the United States, GBS infection is diagnosed in about 5,000 neonates per year, and mortality caused by this microorganism is estimated at ca. 5 %.

Studies on *S. agalactiae* have provided information concerning 27 main surface proteins of this species. They include ornithine carbamoyltransferase (OCT) and protein PGK, which react with antigens directed against them. These proteins are the subject of scientific research aimed at their application during the creation of vaccines against GBS. The studies focused on GBS constitute a very important element allowing the development of methods for the prevention of

diseases caused by this microorganism, since no commercial vaccine protecting against *S. agalactiae* infections has been created so far [4].

The pathogenicity of *S. mutans* is primarily related to the ability of adhesion to host cells. Biofilm formation is a complex process engaging a number of proteins. Khan et al. made a mutation of *S. mutans*, impairing the microorganism's ability to form biofilms. The modified strains were characterized by poorer adhesion to surfaces covered with saliva and by weakened biofilm formation. Confocal and scanning microscope images confirmed that the biofilm in these strains was thinner and looser compared to the biofilm formed by nonimpaired strains. Forty-four proteins, the expression of which is higher in a situation of proper biofilm formation, and 13 proteins of weakened expression were identified using electrophoretic techniques [13]. The described proteins relating to biofilm formation mainly include glycosyltransferases (Gtf), which mediate biofilm matrix synthesis, extracellular polysaccharides (EPS) [14, 15]. As observed by Flemming and Wingender, there is no biofilm without an EPS matrix [16]. The main components of EPS are glucans synthesized from saccharose, which provide the binding sites, and, thus, promote the accumulation of microorganisms and formation of cell clusters or microcolonies on the tooth surface. *S. mutans* produces at least three kinds of glycosyltransferases (Gtf): GtfB is related to insoluble glucan synthesis; GtfC synthesizes soluble and insoluble glucans; GtfD mainly synthesizes soluble glucans. According to Koo et al., GtfB and GtfC are essential for EPS matrix formation, with GtfB being mainly responsible for *S. mutans* aggregation [15] due to its high affinity to bacteria [17], GtfC is adsorbed on the tooth surface, while GtfD acts as a starter for GtfB [17]. Additionally, other surface proteins having an affinity to glucan (glucan-binding proteins, Gbps) contribute to biofilm growth by interactions of *S. mutans* with extracellular glucan. There are at least four groups of glucan-binding proteins, GbpsA, GbpsB, GbpsC, and GbpsD, differing in terms of their affinity to glucan, structure, and immunological properties. Duque et al. proved that GbpsB plays a role in biofilm formation [14]. A microorganism adhering to the enamel via glucan is the main saccharose-dependent way of biofilm formation, but there is also a saccharose-independent mechanism leading to biofilm formation [18]. Aggregation under conditions independent of saccharose is based on interactions between agglutinins present in saliva and P1 adhesins originating from *S. mutans* [18]. Agglutinins present in saliva contribute to the process of *S. mutans* adhesion and aggregation via interaction with antigen I/II, i.e., the multifunctional adhesin P1 (also called AgB, adhesin SpaP, or Pac1) embedded in bacteria cell walls and encoded by the *spaP* gene [13, 18–20].

The family of Ag I/II proteins represented, inter alia, by SpaP, SspA, or SspB proteins is identified not only on the

surface of *S. mutans* but also on other microorganisms, such as *Streptococcus pyogenes*, *Streptococcus agalactiae*, or *Streptococcus suis* [19]. The genetic sequence encoding Ag I/II is composed of six separate regions. The most important of them include region A rich in alanine and region P rich in proline. Region V, which concentrates most of the various sequences observed in particular strains, is localized between them. Regions A and V encode adhesive epitopes occurring on the surface of bacteria cells (so-called adhesintopes), which are responsible for a microorganism's affinity to saliva glycoproteins [21]. The contribution of regions A, P, and V in adhesion was confirmed in a study conducted using mutant strains [19]. None of them demonstrated the ability to adhere to solid surfaces covered with saliva membranes. The expression and biological activity of protein P1 in *S. mutans* also depends on numerous gene products, e.g., genes *luxS*, *ropA*, and *srtA* (an encoding enzyme responsible for adhesin P1 attaching to cell walls) [18, 22].

Protein SpaP, and other proteins from the Ag I/II family, specifically interact with glycoprotein-340 (gp-340), which is present in saliva. It is interesting that gp-340 dissolved in the liquid phase of the saliva participates in bacterial cell aggregation and, thus, eradicates them from the oral cavity. However, when gp-340 is absorbed on the surface of the teeth or gums, it constitutes a receptor for surface bacterial adhesins initiating adhesion processes [18, 19]. The AgI/II family of proteins also participates in interactions between the microorganisms, e.g., *Streptococcus gordonii* and *Porphyromonas gingivalis*, as well as in the aggregation of cells lacking in gp-340 [19]. The key role in interactions between *S. mutans* and saliva agglutinins is played by the specific structure and localization of protein P1, as has been proved thanks to an application of this microorganism's mutant strains (*spaP* and *srtA*). It has additionally been demonstrated that the lack of the expression of genes encoding the sortase A enzyme (SrtA) results in not only an incorrect localization of adhesin P1, but also of other surface proteins, which is significant in the context of bacteria aggregation abilities [18].

The ability of *S. mutans* species bacteria to form biofilm is significant from a clinical point of view not only in the context of caries etiology, but also in cases of endocarditis (IE) [23]. IE development is possible when the formation of a very small clot rich in platelets and fibrinogen occurs as a result of slight damage to the endocardium. When microorganisms reach the blood at this time, they may use this favorable medium for embedding and biofilm formation. Such clots are formed most often at the edge of leaflets of the mitral and tricuspid valves at the side of the atrium, and on the aortic and pulmonary valves at the side of the ventricles [24]. The survival of *S. mutans* in the bloodstream, which it usually reaches after stomatological treatment, is connected to the presence of a few pathogenicity factors on the bacteria surface which have been described in various IE

cases affected by this microorganism. Most importantly, there are those factors responsible for an increase in protein resistance to phagocytosis: a fibronectin-binding protein (so-called autolysin A, AtlA) [25] and a serotypically specific polysaccharide [26]. Next is antigen C, the expression of which results in an increased aggregation of blood platelets and, thus, increased coagulability [27].

The complexity of relationships between microorganisms and hosts, as well as the differentiated expression of the features determining microorganism pathogenicity, mean that pathogenicity is an unpredictable phenomenon. This is due to the fact that, even a complete understanding of both the hosts and the microorganisms does not allow a determination of all possible interactions between them.

Due to an occurrence of some special properties of the hosts and the microorganisms, different kinds of infectious disease varieties are observed more often. The possibilities offered by rapid worldwide travel contribute not only to microorganism transfer in environments not inhabited by them previously, but also enhance their virulence. We often need decades of research on all factors affecting the pathogenicity of microorganisms suspected of causing a given disease in order to link some diseases with their causes. Therefore, constant scientific interest in the interactions occurring between microorganisms and hosts may contribute to a deepening of knowledge concerning the pathogenicity of an increasing number of microorganisms [28].

Pathogenicity of the *Streptococcus* genus

Bacteria of the *Streptococcus* genus include a large number (>100 species) of microorganisms colonizing human and animal mucous membranes. They occur as physiological flora in the oral cavity and intestines of humans and animals. In addition, they often inhabit the skin, throat, and upper respiratory tract. However, numerous streptococci occur as opportunistic pathogens, causing infections in the case of weak immunological response of the host body they occupy. Pathogenic streptococci may be divided into three groups: those commonly causing infections in humans, and commensal and epizootic species which cause disease symptoms under specified conditions [4]. Typical pathogenic species include *S. pneumoniae*, with *S. pyogenes* and *S. agalactiae*. According to the estimations of the WHO, every year, pneumonia resulting mainly from *S. pneumoniae* activity causes ca. 1.2 million deaths of children younger than 5 years of age all over the world, which constitutes 18 % of all deaths in this age group [5, 29]. *S. agalactiae* (GBS) seems to be an equally dangerous microorganism. It is the most often the cause of invasive neonate infections, which occur in the form of sepsis, pneumonia (80 % of cases), or, more rarely, meningitis (10 % of cases) or parthrosis. In 4 % of cases, an infection ends with neonatal

death. It is estimated that ca. 10–30 % of pregnant women are infected with GBS [30, 31]. An introduction of wide-scale prevention caused the frequency of early GBS sepsis occurrence in neonates to drop to 3–4 cases per 10,000 live births in 2010 [32]. Human physiological streptococci which are able to induce opportunistic infections include, e.g., *S. mutans* and *S. intermedius*. Species responsible for opportunistic, epizootic infections are *S. canis* (causing soft tissue infections, urinary tract infections, bacteremia, bone infections, pneumonia), species initially classified as *S. bovis*, especially including *S. equinus*, *S. bovis* (causing endocarditis, bacteremia, meningitis, sepsis) [4]. The consumption of infected milk resulted in some cases of human infections (such as arthritis, endocarditis, meningitis) with epizootic *S. equi* species, a zoonotic subspecies [33] (see Fig. 1).

Streptococci inhabiting the oral cavity

According to the latest reports, *Streptococcus* species normally observed in the oral cavity may be pathogenic. An example may be a case of healthy young men without risk factors, in whom spleen abscess and brain abscess caused by *S. intermedius* were diagnosed [39]. *S. sanguis* streptococci of the Viridans group were the reason for breast implant infection after wide-ranging stomatological treatment [40]. Over 60 cases in which *S. salivarius* was an etiological factor of meningitis as a result of iatrogenic infections have been recorded [41]. Oral cavity streptococci such as *S. sanguinis*, *S. mitis*, and *S. gordonii* were the reason for endocarditis [42–44]. The latest (isolated from the synovial membrane and synovial fluid of a 62-year-old man, and from the synovial membrane of a 78-year-old woman in the second case) was a reason for septic arthritis [45].

Despite the threats related to the above-mentioned bacteria, caries is the most common disease in children. It occurs

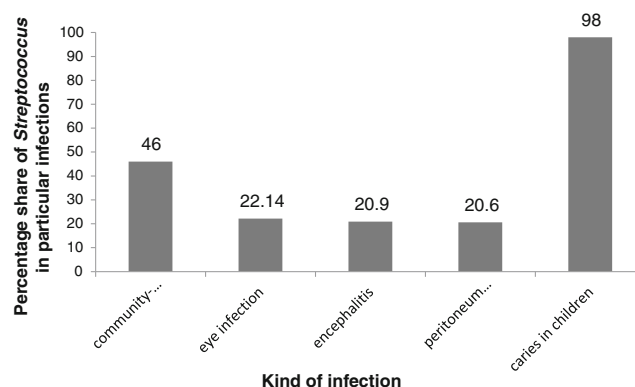


Fig. 1 Percentage *Streptococcus* contribution in particular infections. The diagram was prepared based on the studies of Fontán et al. [34], Bharathi et al. [35], Skoczyńska et al. [36], Juvén et al. [37], and Szczepańska et al. [38]

five times more often than the second disease in the range, i.e., asthma [46]. In Poland, deciduous teeth caries concerns 35–50 % of the children between the second and third years of life, and 56–60 % of the children between the ages of 3 and 4 years. At the age of 6–7 years, deciduous teeth caries is observed in nearly 100 % of children in Poland. Permanent teeth caries in Poland is noted in almost 90 % of children aged 12 years [47]. In the United States, 50 % of children aged 5–9 years have at least one cavity in the tooth or one filling caused by dental caries focus. This number increases up to 78 % by the age of 17 years [46]. Despite numerous research on the etiology and development of the caries, scientists are still not concordant towards some aspects of this disease. Quite recently, *S. mutans* capable of biofilm formation in the oral cavity has been considered as the main factor causing caries [18, 48–51]. However, the fact that the presence of *S. mutans* alone is not sufficient to cause disease development has been the focus of increasing attention currently. The process of dental plaque formation and caries foci development involves, except for *S. mutans*, a few hundred other bacterial species, which, together, form the biofilm structure [17, 46, 52–54]. Except for microbiological factors, caries development also involves genetic, immunological, and environmental factors, including diet [46, 53]. The species having the three main phenotypic features allowing them to survive in the oral cavity environment, i.e., ability of adhesion (and, thus, biofilm formation), ability of acids production, and ability of inhabiting an environment with large pH fluctuations, osmolarity or oxygen availability fluctuations, are considered as equally important species contributing to environment acidification and caries foci formation. These mainly include: *S. sobrinus*, *S. mitis*, *Actinomyces* spp., *Lactobacillus* spp., *Bifidobacterium* spp., and *Fusobacterium nucleatum* [46, 52, 55]. While considering the role of bacterial biofilm in the etiology of teeth and oral cavity diseases, it should be also noted that its occurrence is possible due to specific mutual interactions observed between microorganisms of the same or various species [46, 56]. Attention is focused on the examination of relations observed during biofilm formation and its maturation, development of resistance and wider spectrum of antibiotics, analysis of the microorganism's genome, and mechanisms of specific bacterial protein activity [57–59]. Despite an idea considering *S. mutans* as one of the main cariogenic factors has been abandoned recently, this microorganism is still the main target of scientific research.

S. mutans species may also cause endocarditis and bacteremia [23, 60]. *S. mutans* was isolated from the heart valve in a patient with endocarditis, which had already been described in 1977 [61]. Oral cavity streptococci are correlated with observed endocarditis. This is an important issue from the point of view of the growing resistance to penicillin among oral cavity flora microorganisms (in the case of: *S. mitis* >24 %; *S.*

sanguis >19 %; *S. mutans* >14 %) [62]. *S. mutans* was also a reason for recurring bacteremia in a woman with Sjögren's syndrome [63]. Besides endocarditis and bacteremia, *S. mutans* may also cause sepsis [40]. It is speculated that *S. mutans* may be the cause of other constitutional diseases [64]. Also, a rare case of retroperitoneal abscess caused by *S. mutans* has been described [65].

Sepsis

Streptococcus-caused sepsis is mainly related to severe *S. pneumoniae* and *S. pyogenes* infections. The frequency of invasive infections with *S. pneumoniae* in Poland is 0.78 cases per 100,000 people, while in children below 2 years of age, 5.17 cases are noted; the mortality rate as a result of these infections is 22.6 % [66]. In total, 364 cases of pneumococci-caused diseases were noted in 2010, including sepsis (172 cases), encephalitis and/or meningitis (180 cases), and other, unspecified diseases (63 cases) [67]. In the same year, *S. pneumoniae* was the etiological factor of meningitis in children up to the fourth year of life, and encephalitis in 19.3 % of the patients [68]. In Europe, the frequency of invasive *S. pneumoniae* infections range, depending on the country, from 0.4 to 20 cases per 100,000 people [69]. In the United States, 6.3 cases per 100,000 people are noted in the population below 18 years of age [70]. Such high incidence of the above-mentioned diseases and mortality related to *S. pneumoniae* infections have prompted scientists to an elaboration of vaccines aimed at decreasing the number of incidents. It is known that the main factor of microorganism pathogenicity is the polysaccharide envelope [48], which was the basis of division for over 90 serotypes of the microorganism *S. pneumoniae* [7–9]. Polysaccharide antigens are used in pneumococcal vaccine and are conjugated with proteins in order to enhance immunological response with respect to those which would have been observed during natural infection with bacteria within the polysaccharide envelope [10]. Conjugation of these substances allows an effective immunization of children below 2 years of age, who are a reservoir of numerous opportunistic pathogenic bacteria as this stage of their lives [8]. Many types of *S. pneumoniae* vaccines are distinguished; however, 7-, 10-, and 23-valent vaccines are used the most often. 7-valent vaccine (protein conjugate vaccine, PCV7) contains polysaccharide antigens which were found in seven serotypes of the microorganisms responsible for 80–95 % of invasive pneumococcal infections [49]. Its effectiveness is confirmed by the data collected after the vaccine introduction in the United States—the number of cases of invasive pneumococcal disease among children up to the 5th year of age decreased by 94 % [71]. However, PCV7 does not provide a homogenous effect for all vaccinal serotypes

which it is aimed at. Comparing infections from the period before and after 7-valent vaccine introduction in the United States, the highest decrease in occurrence (three-fold and more) was noted for serotypes 14, 9V, and 23F. A two-fold decrease in the frequency of occurrence was observed for serotypes 18C and 6B, while the lowest decrease was noted for serotype 19F. The number of infections caused by nonvaccinal serotypes was to be concurrently increasing.

Similar trends were observed in the case of strains resistant to antibacterial substances. At the moment of vaccines introduction, resistance among vaccinal serotypes decreased about 1.5-fold, while the resistance of nonvaccinal serotypes was doubled. An increase in the number of noninvasive serotypes resistant to two or more antimicrobial factors was also observed [7]. Poland introduced PCV7 to the vaccinations schedule in 2008, together with 22 other countries. In turn, 10-valent vaccine obtained pre-qualification from the WHO in 2010 [8]. It may be concluded from the official data, that the number of people vaccinated against pneumococci in Poland increased from 148,664 in 2009 to 155,258 in 2010. Despite this, incidences of disease related to this pathogen infection have not decreased [68].

Conjugated 13-valent vaccine (PCV13) of widened spectrum of activity has been created as a response to an increasing number of infections caused by nonvaccinal serotypes [8]. It is composed, except for antigens used in PCV7, of six additional polysaccharide antigens characterizing further *S. pneumoniae* serotypes, and they were combined with the same membrane protein, CRM197. These serotypes have been observed most often in Africa, Asia, and Latin America, and are consistent with serotypes causing 70 % of invasive pneumococcal infections all over the world. It was also demonstrated during the research that PCV13 may also

be used in children infected with the human immunodeficiency virus (HIV) virus, which, to a certain extent, protected them against pneumococcal infections. The 13-valent vaccine was introduced in over 40 countries; however, there is still a lack of documentation related to this vaccine's influence on the spread of infections caused by *S. pneumoniae* around the world, confirming a decrease in cases caused by *S. pneumoniae* serotypes used in the vaccine [8].

Vaccine against *S. pneumoniae* targeted towards the highest number of serotypes of this microorganism is polysaccharide 23-valent vaccine (PPV23). It demonstrated weak immunogenicity towards children; however, it gained wide application in risk groups and among older people [9]. This polysaccharide vaccine is not conjugated with protein, and, therefore, should not be administered in children less than years of age, and it has been recommended since 2000 that PPV23 should follow PCV7 vaccination [6].

Investigators suggest [9] that *S. pneumoniae* serotypes such as 11A, 31, 10A, and 9N should be treated in a prioritized manner in the creation of new vaccines against this pathogen, since they are responsible for the highest number of infections caused by nonvaccinal serotypes.

The next significant reason for diseases occurrence and mortality all over the world is invasive GAS infections. *S. pyogenes* is responsible for ca. 700 million infections each year, causing about 500,000 deaths [11]. In Europe, they are noted with varying frequencies per 100,000 people: 3.12 cases in Great Britain [72]; 3.1 in France [73]; as much as 3.9 in Finland [74]. The mortality rate as a result of GAS infection in these countries is 19, 14, and 9 %, respectively. In the United States, the frequency of invasive GAS infections is similar: 3.5 cases per 100,000 people, with a mortality rate of 12.5 % [75] (see Fig. 2). GAS strains are concurrently responsible for ca. 18 million cases of rheumatic heart

Fig. 2 Number of cases of invasive pneumococcal disease caused by *Streptococcus pneumoniae* over the years in Europe, using Denmark as an example. The diagram was prepared based on the studies of Harboe et al. [76] and Ingels et al. [77]

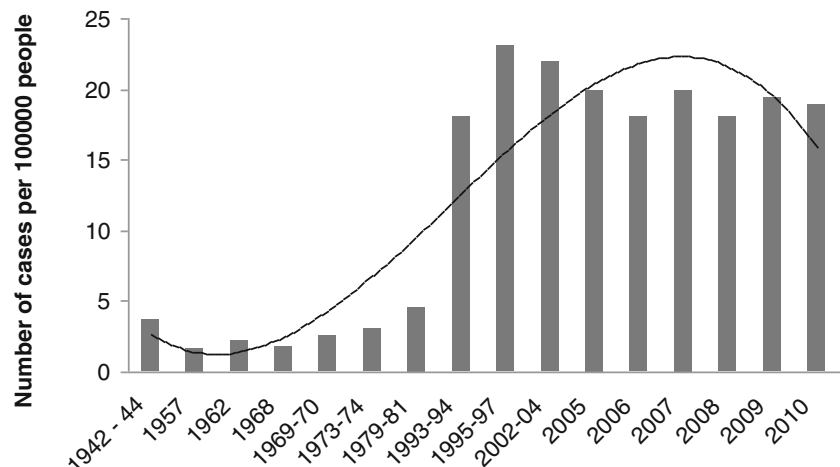


Table 1 Cases of infections caused by *Streptococcus* spp.

Species	Patient (n) age/sex	Risk factors	Therapy	Decease	References
Cases of bacteremia and general infections					
<i>Streptococcus viridans</i>	45/M	Teeth and gums disease	Ill teeth extraction	N	[81]
<i>Streptococcus salivarius</i>	n=30 22/M	Endocarditis		3	[82]
Group C <i>Streptococcus</i>	n=88	Basic disease 72.7 %	β-lactams	25 %	[83]
<i>Streptococcus pneumoniae</i>	n=590	Intravenous drug abuse, infectious metastases, purulent vein inflammation, endocarditis		19 %	[84]
<i>Streptococcus</i> spp.	n=100 20–40/F			6	[85]
<i>Streptococcus pneumoniae</i>	n=55 0–5 years		Amoxicillin, clarithromycin, azithromycin, ceftriaxone, cefibuten, cefaclor		[86]
<i>Streptococcus pneumoniae</i>	n=71 42/M	HIV	Third-generation cephalosporins, vancomycin, or erythromycin	28 %	[87]
<i>Streptococcus</i> spp.	n=522				[88]
Viridans group <i>Streptococcus</i>	n=79 (88 episodes)	Leukemia/stem cell transplantation	Piperacilin and gentamicin, piperacilin and tobramycin, or ceftazidime and tobramycin		[89]
	<18 years of age		The most often used empiric therapy: piperacilin and tobramycin (75 % of episodes)		
<i>Streptococcus agalactiae</i>	21 days/F		Ceftriaxone	N	[90]
<i>Streptococcus anginosus</i>	46/M	Uremia, hypertension, recurrent infections	Ceftriaxone, vancomycin	N	[91]
<i>Streptococcus viridans</i>	n=15 <20 year of age	Hematological cancers			[92]
<i>Streptococcus</i> spp. (in addition to <i>S. pneumoniae</i>)	n=30 59 years (average)	Community-acquired infections		3	[93]
	15/M				
Cases of encephalitis					
<i>Streptococcus mutans</i>	60/M	Medical treatment	Penicillin G		[94]
<i>Streptococcus bovis</i>	53/M	HIV	Penicillin G		[95]
<i>Streptococcus pyogenes</i>	41/F		Ceftriaxone, vancomycin	Y	[96]
<i>Streptococcus gallolyticus</i> subsp. <i>pasteurianus</i>	5 days/F		Cefotaxime	N	[97]
<i>Streptococcus gallolyticus</i> subsp. <i>pasteurianus</i>	75/M		Ceftriaxone and dexamethasone	N	[98]
<i>Streptococcus pneumoniae</i>	16 days/F 1/M	Acute retina hemorrhage		Y	[99]
<i>Streptococcus equi</i> subsp. <i>zooepidemicus</i>	79/M	Trampling by horses	Vancomycin, metronidazole, ceftriaxone	N	[100]

Table 1 (continued)

Species	Patient (n) age/sex	Risk factors	Therapy	Decease	References
<i>Streptococcus equi</i> subsp. <i>zooepidemicus</i>	n=20 13–87 years 57.7% M	Close contact with animals, mainly horses	Benzylopicillin, cephalosporins	24 %	[100]
<i>Streptococcus agalactiae</i>	67/M	Meningitis	MEPM, VCM, linezolid		[101]
<i>Streptococcus pneumoniae</i>	n=203 Children	State of compromised immunity; acute disease	Prematurity	9.4 %	[102]
	n=7/65 Adults		Smoking; age>65 years	17.5 %	
<i>Streptococcus pneumoniae</i>	n=548		Penicillin, third-generation cephalosporins, ampicillin	37 %	[103]
<i>Streptococcus suis</i> serotype 2	n=101	Geographical (the most common reason for meningitis in Vietnam)			[104]
<i>S. galloyticus</i> subsp. <i>pasteurianus</i>	n=4 <2 weeks				[105]
<i>Streptococcus salivarius</i>	n=65	Iatrogenic 67 %, cerebrospinal fluid leak (head injury, neurosurgical treatments) 21 %	Beta-lactams (penicillin or cephalosporin), vancomycin	2	[58]
<i>Streptococcus intermedius</i>	70/F	Lack	Carbapenems, vancomycin, ceftriaxone, ampicillin	N	[106]
<i>Streptococcus pneumoniae</i>	n=3 Adults	Meningitis; long-term neurological deficit			[107]
Cases of eye infection					
<i>Streptococcus mitis</i>	85/M	Complicated endocarditis	Vancomycin, amikacin, levofloxacin, ampicillin, ceftriaxone, gentamicin	N	[108]
<i>Streptococcus uberis</i>	52/M	Postoperative endophthalmitis	Ceftazidime, vancomycin, dexamethasone, ampicillin, moxifloxacin	N	[109]
<i>Streptococcus bovis</i>	47/M	Alcoholism	Vancomycin, ceftazidime, dexamethasone	N	[110]
<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	50/F 75/M	Eye surgery	Cefazolin, amikacin, ofloxacin, tobramycin	N	[111]
<i>Streptococcus pneumoniae</i>	62/M	Iatrogenic infection			
	n=32 <2 years of age	Lack of vaccination against <i>S. pneumoniae</i> /Young age of the patient			[112]
<i>Streptococcus mitis/oralis</i>	n=12	Endophthalmitis after antibiotic administration to the vitreous humor	Bevacizumab		[113]
Cases of peritoneum inflammation					
<i>S. viridans</i> 90 %	n=68	Peritoneum dialysis	Cefazolin and vancomycin	N	[114]
<i>S. agalactiae</i> 2 %					

Table 1 (continued)

Species	Patient (n) age/sex	Risk factors	Therapy	Decease	References
<i>S. bovis</i> 2 % Nonhemolytic <i>Streptococcus</i> 6 %	58.7 % M (104 episodes of peritoneum inflammation)				
<i>Streptococcus bovis</i>	75/M	Cirrhosis caused by alcohol abuse	Ceftriaxone	Y	[115]
<i>Streptococcus agalactiae</i>	52/F	Peritoneum dialysis	Ceftazidime, tobramycin, vancomycin	N	[116]
<i>Streptococcus pyogenes</i>	23/F	Lack	Ceftriaxone, metronidazole, levofloxacin, amoxicillin	N	[117]
<i>Streptococcus pneumoniae</i>	38/M	Hepaticcirrhosis and ulcers (as a result of alcohol abuse)	Third-generation cephalosporins	N	[118]
<i>Streptococcus mitis</i>	54/F	Previous <i>S. pneumoniae</i> infections			[119]
<i>Streptococcus gordonii</i>	69/M	Peritoneum dialysis	Cefazolin	N	[120]
<i>Streptococcus bovis</i>	n=20 (23 episodes)	Peritoneum dialysis		N	[121]

F female, M male, Y yes, N no

disease. resulting in a death of ca. 500,000 people each year. A considerable relationship between GAS strains causing pharyngitis in children and the strains related to invasive disease in society was also observed. These data suggest that schoolchildren may constitute a reservoir of infections for society [78–80].

One of the most common *S. pyogenes* strains is M1T1, which is responsible both for pharyngitis and more severe states, such as necrotizing fasciitis or toxic shock syndrome. This bacterium is equipped with flagella referred to as antigen T. However, unlike in the case of flagella noted in *S. pneumoniae*, their presence in *S. pyogenes* causes a decrease in the invasiveness and pathogenicity of the strain. Despite the similarity of both kinds of flagella in general and their main genetic structure, small differences in particular genes enable functional diversity of encoded proteins. The flagella of M1T1 strains increase the adhesive properties of bacteria towards the endothelial tissue; however, they concurrently constitute molecular standards for phagocytic cells of the host, and, thus, are exposed by their increased activity and faster elimination from an organism [12] (see Table 1).

Despite the wide range of GAS-related research, no licensed vaccine against this group of microorganisms has been created so far [11]. This is affected by, e.g., large serotype differentiation of protein M, which was the hope for an application in vaccines at the beginning of the 21st century [4, 11]. A formulated 6-valent vaccine against GAS containing N-end parts of six serotypes of protein M provided a desirable effect in tests on animals—an increase in the antibodies index against antigens contained within it. An increase in the antibodies index was also demonstrated in the initial phase of clinical studies, and, additionally, no cross-reactions with human tissues were observed. The vaccine is subject to further tests; however, it is considered that its disadvantage is protection against only 6 among 120 suggested serotypes of protein M [4]. The development of genetic studies conducted on *S. pyogenes* may, in the future, allow to elaborate on the methods which will help identify antigens suitable for application in vaccines. Such research has been conducted in silico [11]. The result was an identification of genes for 309 surface proteins, among which at least 260 were present in 6 among the 8 examined strains that were selected. Subsequently, 147 proteins for which it was possible to establish the topology on the microorganism cell surface were selected, and their origin was established. It appeared that many of these proteins constitute the virulence factor of *S. pyogenes*. The analysis of 81 among 147 genes demonstrated that 82 % of them were present in all the examined GAS isolates, while 73 of

Table 2 Other infections caused by *Streptococcus* spp.

Species	Infection	Patient (n) age/sex	Risk factors	Therapy	Decease	References
<i>Streptococcus sanguis</i>	Liver abscess	39/M	Mucous membrane biopsy	Penicillin G, metronidazole, ampicillin	N	[122]
<i>Streptococcus salivarius/oralis</i>	Rhabdomyolysis	25/M		Ampicillin, cefmetazole, furosemide	N	[123]
<i>Streptococcus pyogenes</i>	Hemolytic-uremic syndrome	7 months/F 11 months/M	Pneumonia	Cefotaxime and vancomycin	Y N	[124]
<i>Streptococcus pyogenes</i>	Septic shock	39/F	Influenza B	Piperacillin, tazobactam, oseltamivir, high doses of penicillin, clindamycin, immunoglobulins	N	[125]
		27/F		Amoxicillin, clavulanic acid, clarithromycin, catecholamines, high doses of penicillin, oseltamivir	Y	
		61/F		Amoxicillin, ceftriaxone, clarithromycin, vancomycin, oseltamivir	N	
<i>Streptococcus pyogenes</i>	Spine abscesses	70	Influenza	Meropenem and clindamycin, then penicillin G and clindamycin	Y	[126]
<i>Streptococcus intermedius</i>	Liver abscess	27/M	Chronic granulomatous disease	Amoxicillin, penicillin G	N	[127]

them (90.12 %) were noted in over 80 % of isolates. As a result, 52 proteins which may constitute a target for future research have been presented. Genetic examination is an approach for the creation of vaccine against GAS, since they considerably widen the list of surface antigens which may be used for the process. Additionally, they confirm an occurrence of particular proteins in numerous bacterial strains, which may point towards the success of vaccinations all over the world. It was also established, as a result of the studies conducted, that serotype M1 is less invasive than M49; however, this needs to be verified by additional research [11] (see Tables 1 and 2).

New species

Pathogenic species of the *Streptococcus* genus were isolated and described as early as by the end of the 19th century [128, 129]. Subsequently, new species have been discovered and described: Hardie and Whiley in 1997 reported about ca. 40 species [130]; 10 years later, ca. 50 species were known, and most of them were pathogenic for humans [4]. Certainly, this number is not definitive. An example is *S. tigurinus*, a species discovered this year by Swiss researchers, and present in the oral cavity as physiological flora; however, it may be responsible for endocarditis and meningitis [131]. Another example is a new subspecies of *S. gallolyticus* identified in 2003, i.e., *pasteurianus* [132], described for the first time as an etiological factor of meningitis in an infant in 2009 (see Table 1) and in an adult in 2010 (see Table 1). Another species is *S. urinalis*—a case of bacteremia caused by this pathogen [133] was described in a 60-year-old man with urethral stricture history. *S. australis*, described initially as one of the oral streptococci [134], also appeared to be an etiological factor in the case of meningitis [135]. An example of the species responsible for a range of human and animal infections (responsible for the spontaneous fermentation of dairy products in Africa) was *S. infantarius* subsp. *infantarius* (Sii) belonging to *S. bovis/S. equinus*, exhibiting 80 % similarity to the *S. thermophilus* genome [136].

Summary

Infections with bacteria of the *Streptococcus* genus play a significant role from a clinical point of view. Firstly, the infections are of varying character, from local to severe general infections (see Tables 1 and 2). Secondly, the pathogenicity of the *Streptococcus* genus is

connected not only to “classical” pathogens, but cases of opportunistic infections are also described more often, e.g., species physiologically inhabiting the oral cavity (*S. intermedius*, *S. salivarius*), where injuries or surgical treatments may cause infections, and, worryingly, cases of meningitis caused by *S. intermedius* without previous risk factors have been reported [39]. Additionally, streptococci are identified as one of the main etiological factors of such severe diseases like pneumonia, meningitis, or peritoneum inflammation, and also diseases of a social character, like caries (see Fig. 1). Caries appears to be a huge problem and, unfortunately, there is a lack of suitable knowledge in the society concerning risk factors (see Table 3), which results in 87 % of caries in children in Poland alone [148]. Comparing the results of CDL indices in 12-year-old children for European countries, Poland is placed in the next to last position (CDL=4.4), the best dentition state is noted for children in Holland (CDL=0.9), while the highest index was noted in Latvia (CDL=7.7) [47]. In the United States, 50 % of children aged 5–9 years have at least one cavity in their teeth [46].

Due to long-term research which has broadened the scientific understanding of the virulence of specific pathogens, scientists are able to create new vaccines,

which are oriented toward specific substances or antigens occurring on the surface of given microorganisms. This allows increased effectiveness in the fight against infections caused by, e.g., *S. pneumoniae*. The Centers for Disease Control and Prevention (CDC), WHO, and National Institute of Hygiene, Poland (PZH) reports reveal that the number of people vaccinated against pneumococci has been increasing (in Poland, it grows each year—from 2007 to 2011, the number of those vaccinated increased by as much as 78,500) [5, 32, 149]. This points to increased awareness within society and the application of pneumococcal infections prophylaxis. Despite this, morbidity-related infections caused by this pathogen are not decreasing, and this is connected to the new and pressing problem faced by the medical world, i.e., the growing number of dangerous nonvaccine strains causing an increasing number of infections in humans [7].

In the light of new taxonomic reports, differentiation of the increasingly growing number of species and subspecies, as well as the latest descriptions of cases of particular species of *Streptococcus* infections, the pathogenicity connected to the *Streptococcus* genus is still not fully recognized and should be the subject of further studies.

Table 3 Caries in children caused by *Streptococcus* spp.

Species	Patient (n) age/sex	Risk factors	References
<i>S. mutans</i>	n=133 1–4 years	Falling asleep with a bottle Improper hygiene of the oral cavity	[137]
<i>S. mutans</i>	n=3531 4–11 years	Passive smoking	[138]
<i>S. mutans</i>	Children <3 years	Vertical and horizontal transmission Frequent meals consumption, pulpy consistence of meals Improper nutrition of pregnant mother Early appearance of teeth weaken saliva secretion, composition of saliva different to in adults	[139]
<i>S. mutans</i>	n=156 mother–infant pairs	Caesarean section	[140]
<i>S. mutans</i>	n=109 3 years	Caesarean section	[141]
<i>S. mutans</i> and <i>Lactobacillus</i> spp.	Children <6 years	Vertical and horizontal transmission Frequent consumption of sugars	[142]
<i>S. mutans</i>	Children	Transmission in early period of life Dietary factors	[143]
<i>S. mutans</i> and <i>S. sobrinus</i>	n=54 2.5 years	<i>S. mutans</i> and <i>S. sobrinus</i> in mother	[144]
<i>S. mutans</i> and <i>S. sobrinus</i>	n=30 Children	“Sticky desserts” Higher socioeconomic status (data from Sudan)	[145]
<i>S. mutans</i>	1–6 years	<i>S. mutans</i> in mother	[146]
Streptococci from <i>Streptococcus mutans</i> group		Psychosocial, behavioral factors	[147]

Conflict of interest All authors confirm that there is no conflict of interest.

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