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Streptococcal infections: Race to multidrug resistance—A review

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ABSTRACT

According to the World Health Organization, the bacterial resistance to antimicrobial drugs has emerged as one of the major universal problems that requires and needs prime attention by humankind due to the emerging resistant acquired by many of the bacterial species which allows them to evade both antimicrobial drugs and the immune system. *Streptococcus* species (e.g., *Streptococcus pneumonia*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*) are categorized serologically and are grounded on carbohydrates present in the cell wall into different groups, such as Group A to Group V. There are over 85 capsule antigenic types of *S. pneumoniae*, 124 serotypes of *S. pyogenes*, and 9 *S. agalactiae* with capsular polysaccharide serotypes (CPS). The primary cause for the failure of treatment for *streptococcal* infections is the enhanced resistance to antimicrobial drugs. Recently, infections caused by *Streptococci* resistant to multiple drugs have been increasing with a substantial affect to public health. Among *Streptococcus* species, drug resistance develops due to the excessive use of antibiotics. *Streptococcus* strains are also known as biofilm markers. The improved resistance of biofilms to antimicrobials among *Streptococcus* species stimulates persistent infection, which includes around 80% of bacterial infections in people. This review mainly focuses on the problem concerning *Streptococcus* species that is categorized and prioritized by the WHO.

INTRODUCTION

Resistance to antimicrobial agents among numerous microbes (pathogens) has increased at an alarming rate around the world, posing a serious threat to human health. Because of the emergence of new resistant mechanisms and a decline in the efficacy of infectious disease therapy, microbial responses to routine treatment fail have resulted in longer sickness, higher healthcare costs, and a significant risk of mortality (Arsene *et al*., 2022; Rihana *et al*., 2021). In 2011, the WHO declared "combat drug resistance: no action today, no cure tomorrow." Recently, certain strains of multidrug-resistant microorganisms have quadrupled worldwide (Cohen *et al*., 2020; Sharma *et al*., 2011). Antimicrobial resistance (AMR) is currently posing a greater threat to humans by increasing hospital stays, morbidity, mortality, and severe economic loss to the patient and the nation (Morales *et al*., 2012; Rihana *et al*., 2021; Rosenberger *et al*., 2011). Over the most recent 20 years, there was exceptional expansion in microbial diseases that the norm of overall public health in many regions of the world is currently like those of the pre-antibiotic period (Magiorakos *et al*., 2012). According to the standardized global definitions created by the Centre for Disease Control and Prevention (CDC) and European Centre for Disease Control, the pandrug-resistant (PDR), extensively drug-resistant (XDR), and multidrug-resistant (MDR) microbes have been fairly described (Basak *et al*., 2016). MDR microbes are strains which acquire resistance to a minimum of one drug in several kinds of antibiotic groups (Divya and Vijey, 2017). XDR microbes are strains which acquire resistance to a minimum of one drug in all but two or fewer antibiotic groups (i.e., these strains remain

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vulnerable to only one or two antibiotic groups). PDR microbes are strains resistant to all antimicrobial drugs in all antibiotic groups (Pelluri *et al*., 2022).

It is well implicit that microbes are one of the smartest organisms which can not only stimulate recent techniques incessantly to circumvent the immunological system and antimicrobial agents, but also become accustomed to numerous circumstances to safeguard its existence and growth (Tacconelli *et al*., 2018). By prospecting this, it is essential to understand their mechanism and to come up with a clear knowledge of how they do this and through which kind of function. Nevertheless, it would seem sensible to address all these attempts to certain alarming microorganisms which are resistant by ordering them according to specific conditions. To accomplish this, the WHO issued a list of drug-resistant microorganisms, which has worldwide main concern to enable a way that will guide investigators around the globe and where the necessity of acquiring innovative therapies is essential. Along with the support of expert belief and established statistics, the WHO's microbial list of international importance established a multi-criteria decision analysis procedure for focusing on the research and development of innovative and successful antibiotic therapies. A list of the 12 most dangerous and resistant bacteria families was given with the help of researchers all around the globe based on wherever necessary new therapies are required. The three foremost bacteria were considered a critical priority, and they are *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. The later six bacteria were considered high-ranking priority, and those are *Enterococcus faecium*, *Staphylococcus aureus*, *Helicobacter pylori*, *Salmonella* spp., *Campylobacter*, and *Neisseria gonorrhoeae* (Luepke *et al*., 2016). The final three bacteria were considered moderate priority, and they include *Haemophilus influenzae*, *Staphylococcus pneumoniae*, and *Shigella* spp (Toit *et al*., 2014). These microorganisms were selected based on 10 criteria, which included "mortality, healthcare and community burden, a prevalence of resistance, a 10-year trend of resistance, transmissibility, preventability in the hospital and community settings, treatability and current pipeline" (Luepke *et al*., 2016). The goal of this review is to highlight the current knowledge of the resistance mechanisms acquired in the *Streptococcus* species. This will emphasize mainly on the multidrug-resistant *Streptococcus* species and discuss alternatives or advancements to current antibiotic treatments for the *Streptococcus* species.

ABOUT *STREPTOCOCCUS* SPECIES

The strains of *Streptococcus* are microorganisms belonging to the Firmicutes phylum below the order of Lactobacillales and belonging to the Streptococcaceae family (Anon *et al*., 2018). Triad genera existing in the Streptococcaceae family include *Streptococcus*, *Lactovum*, and *Lactococcus*, and among these, *Streptococcus* species is extremely distinctive, comprising around 79 species (Anon *et al*., 2018). Few of the species of *Streptococcus* are infective to animals and humans, with *S. pyrogens* and *S. pneumoniae* being the extremely crucial pathogens. The strains of *Streptococcus* are Gram-positive microbes that mostly become visible as chains or pairs and ovoid to spherical in appearance, with a nutritionally demanding fermentative metabolism, and several of these varieties form capsules (Hayes *et al*., 2001).

The *Streptococcus* strains are usually found in the nasopharynx and oral cavity and make up a crucial portion of the normal microbiota of individuals and animals (Davis, 1996; Hayes *et al*., 2001). In healthy individuals, the microbiota is harmless; however, they can cause infections in specific instances, for example, immunocompromised stage (Hayes *et al*., 2001; Mitchell, 2003). The strains of *Streptococcus* species (e.g., *S. pneumoniae*, *Streptococcus pyogenes*, and *S. agalactiae*) can be categorized serologically by considering carbohydrates and glycoproteins present in the cell wall into various groups, like Group A to Group V (Hayes *et al*., 2001; Nobbs *et al*., 2009; Patterson, 1996). *Streptococci* are categorize based on structural variations, pili-associated protein with cell wall, biochemical reactions, type of hemolysis using blood agar media, and the presence of a capsule made of polysaccharide (particular for group B *Streptococci*) (Facklam *et al*., 2002). Figure 1 shows the Lancefield classification of *Streptococcus* species. Till now, there are more than 85 capsule antigenic types of *S. pneumoniae*, around 124 serotypes strains of

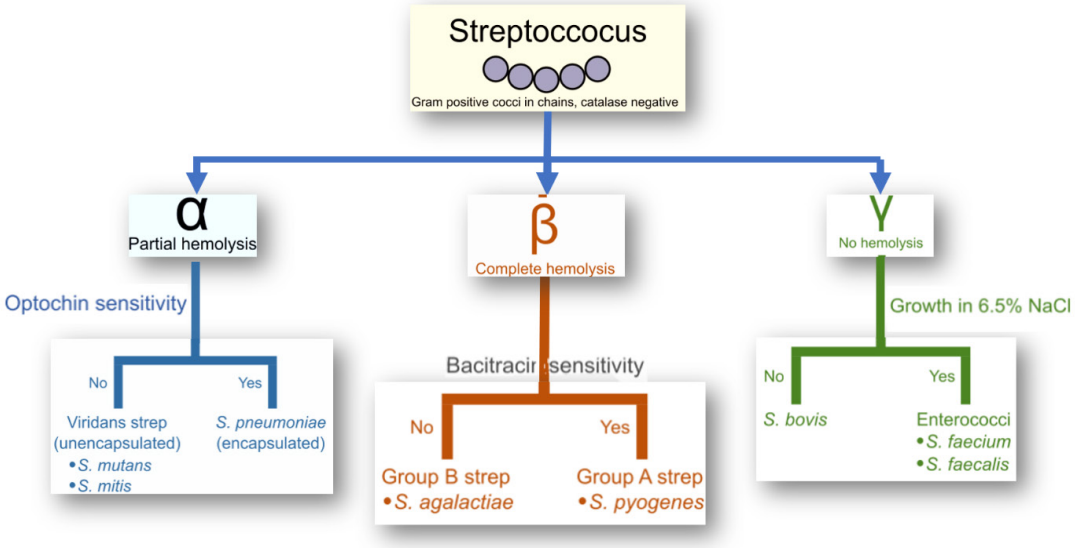

Figure 1. Lancefield classification of the *Streptococcus* species.

S. pyogenes, and 9 CPS of *S. agalactiae* have been recommended (Boyer, 2016; Facklam *et al*., 2002; Zapun *et al*., 2008). The cell wall of *Streptococci* is among the highly researched bacterial cell walls (Cole *et al*., 2008; Facklam *et al*., 2002).

Streptococcal genus—pathogenicity

Different species of the *Streptococcus* genus consist of a substantial number (more than a hundred) of bacteria residing in mucous membranes of human beings and animals. These species appear as biological flora in the buccal cavity and bowels. In supplement to this, these organisms frequently populate the upper respiratory tract, skin, and throat. However, various strains of *Streptococci* occur as unscrupulous pathogens, triggering infectious deceases in the host which have weak immunological reaction. Pathogenic *Streptococci* can be divided into three categories, which are those frequently affecting humans, commensal, and epizootic species that trigger symptoms of infection under circumstances (WHO, 2013).

Corresponding to the opinions of the WHO, nearly 1.2 million newborns die every year because of pneumonia, and the major cause of infection is *S. pneumoniae*, which represents 18% of infant deaths (Sharma *et al*., 2012). The successive major frequent cause of contaminations and global mortality are intrusive group A streptococcal (GAS) diseases. However, *S. pyogenes* is accountable for about 700 million infections every year, leading to the mortality of about 0.5 million people (Cunningham, 2020). Group B streptococcal (GBS) infections, *S. agalactiae*, develop as an equivalently critical microorganism that is accountable for miscarriages, and might as well represent a possibility of early births and neonatal infections of pneumonia type, meningitis, or sepsis (WHO, 2013). Group B *Streptococcus* infections are identified in about 5,000 neonates every year, with an estimated mortality of 5%. Table 1 presents the various pathogenic species of *Streptococcus* and their clinical manifestations of human infections.

RESISTANCE MECHANISM IN *STREPTOCOCCUS* SPECIES

AMR pathways are complex and several mechanisms may exist in the same strain, producing a multidrug-resistant phenotype. The following are some of the basic biochemical processes of AMR: (i) enzymatic inactivation of antibiotics, such as lactamases; (ii) changes of the antibacterial target, such as genome and RNA alterations, which hinder efficient antibiotic binding (e.g., rRNA mutations associated with resistance to several antibiotics); and (iii) limiting drug access to targets, for example, by reducing cell absorption via a decrease in outer membrane permeability in Gram-negative bacteria and/or increasing clearance from within the cell via active efflux pumps.

Various plasmids found in *Streptococcus* are linked to the transmission of antibiotic resistance and pathogenicity. A large number of transposons, including Tn3-family transposons, composite, and conjugative transposons, have been found in *streptococci* in addition to plasmids. Tn916, which encodes tetM, a ribosomal protection protein, has been linked to the independent resistance transfer between a variety of strains via plasmids, including *Enterococcus faecalis*, *S. aureus*, *S. pneumoniae*, *S. agalactiae*, and Streptococcus dysgalactiae subspecies dysgalactiae isolates, which act as reservoirs of functional antibiotic resistance genes.

Various mechanisms of AMR have already been reported in pyogenic *streptococci*, the major mechanisms of action and associated resistances of which will be briefly reviewed (Alves *et al*., 2020). The primary mechanisms of resistance in *Streptococcus* species are shown in Figure 2.

RESISTANCE PATTERNS IN *STREPTOCOCCUS* SPECIES

In this section, the most relevant *Streptococcus* species responsible for the resistance to selected antibiotics, like macrolides, streptogramins B tetracyclines, lincosamides, β-lactams, fluoroquinolone, and integrative and conjugative elements, are discussed.

GROUP A: In this group, the strains of *Streptococcus* have distinct environmental sources, and some of these species are differently tailored to a distinctive host as characterized by β-hemolytic *S. pyogenes*, which is believed as the utmost infective kind of *Streptococcus* species. Together with *S. pneumoniae*, it is accountable for infections like erysipelas, pharyngitis, and other invasive infections, like soft rheumatic fever, tissue infection, streptococcal toxic shock syndrome (STSS), and glomerulonephritis (Carapetis *et al*., 2005; Gillespie, 1998).

Resistance patterns of *S. pyogenes*

Despite the fact *S. pyogenes* has remained commonly vulnerable to β-lactams ever since the 1940s, a considerable number of ineffective treatments have been recorded worldwide (Markowitz *et al*., 1993). A meta-analysis on microbiological rates of ineffective treatment in *S. pharyngotonsillitis* was found to be around 12% during 1953–1993 (Brook *et al*., 2013). During the last two decades, the percentage of penicillin resistance has significantly boosted to about 40% in some regions of the world (Kebede *et al*., 2021). The major justifications for treatment failures with penicillin include: (i) perseverance in intracellular region of *S. pyogenes* because of poor diffusion of this drug into tonsillar tissues spaces, with tonsillar epithelial cells; (ii) coaggregation between *S. pyogenes and M. catarrhalis*, which may develop colonization of *S. pyogenes* through with the help of its adherence epithelial cells in human beings; (iii) protection of *S. pyogenes* by β-lactamase-producing microorganisms (specifically *Haemophilus spp, Moraxella catarrhalis*, *Staphylococcus aureus*, and some anaerobes) that are generally a part of the human microbiota; and (iv) changes of the commensal microbiota, which can strive for nutrients. *S. pyogenes* resistance to macrolides is primarily caused by Erm(B) or Mef(A). Erm(B) is the most important sign of high-level macrolide resistance, whereas Erm(A) solely reflects limited macrolide resistance. *S. pyogenes* resistance to macrolides varies from 2% to 19%, depending on the location. Although other investigations from 2002 to 2012 found no GAS resistance to ceftriaxone, two isolates (5.3%) of GAS in some studies had a higher MIC to this antibiotic, which could be attributable to ceftriaxone overuse (Berwal *et al*., 2019). The AMR patterns of *S. pyogenes* for various antibiotics are shown graphically in Figure 3, among which *S. pyogenes* attained more resistance to Clindamycin (around 50%) and less resistance to Chloramphenicol (about 7.1%) (Ishida *et al*., 2008).

Resistance patterns of *S. pneumoniae*

Among all *Streptococcus* species, *S. pneumoniae* is the utmost frequent basis for community-acquired respiratory

Table 1. Pathogenic *Streptococcus* species and its clinical manifestations.

Name of the species	Serological Lancefield group	Clinical observations	References
S. pyogenes	Group A	Pyoderma, pharyngitis, erysipelas, necrotizing fasciitis, bacteremia, streptococcal toxic shock syndrome, pneumonia, septicemia, meningitis, septic arthritis, scarlet fever, and autoimmune neuropsychiatric disorders	(Carkwright, 1997; High *et al*., 2005)
S. agalactiae	Group B	Septicemia, pneumonia, meningitis, cellulites, osteomyelitis, septic arthritis, meningitis, bacteremia, and necrotizing fasciitis in neonates and infants.	(Lim *et al*., 2007; Schuchat, 1998; Shet *et al*., 2004)
S. pneumoniae	Viridans	Otitis media, meningitis, septic arthritis, pneumonia, septicemia, pleural empyema, and acute conjunctivitis	(Bert *et al*., 1998; Orihuela *et al*., 2006)
S. anginosus	Viridans	Meningitis, septicemia, bacteremia, endocarditis	(Chang *et al*., 2002)
S. constellatus	Viridans	Bacteremia, abscess, endocarditis, and septicemia	(Clarridge *et al*., 2001)
S. intermedius	Viridans	Respiratory infections, including pneumonia, pulmonary abscess, pleural empyema and bacteremia, endocarditis, and septicemia.	(Beighton *et al*., 1994)
S. salivarius,	None	Endocarditis and bacteremia	(Cunliffe *et al*., 1977)
S. vestibularis	None	Endocarditis and bacteremia	(Doyuk *et al*., 2002; Han *et al*., 2006)
S. mitis	Viridans	Upper respiratory infection, bacteremia, septicemia, and endocarditis (instigated by *S. sanguis*	(Cunliffe *et al*., 1977; Douglas *et al*., 1993)
S. oralis			(Westling *et al*., 2002)
S. cristatus			(Herzberg *et al*., 1997) (Bochud *et al*., 1994)
S. gordonii			(Han *et al*., 2006)
S. parasanguis			(Woo *et al*., 2004)
S. sanguis			(Whiley *et al*., 1999)
S. sinensis	None Viridans	Bacteremia, endocarditis Pharyngitis	(Hashikawa *et al*., 2004)
S. constellatus			(Teare *et al*., 1989)
S. dysgalactiae subsp. equisimilis,	Group C	Bacteremia, pharyngitis, endocarditis, septicemia, and septic arthritis,	(Bordes *et al*., 2006)
			(Yuen *et al*., 1990)
S. equi subsp. Zooepidemicus	Group G	Pharyngitis, pneumonia, bacteremia, meningitis, septicemia, endocarditis, septic arthritis, toxic shock syndrome, and glomerulonephritis	(Francis *et al*., 1993)
			(Barnham *et al*., 1987)
			(Gerber *et al*., 2006)
S. bovis	Group D	Endocarditis, bacteremia, meningitis, and septicemia *Streptococcus bovis* and *Streptococcus infantarius* are the reasons for acute inflammatory gastrointestinal disorders and play a probable role in colon carcinogenesis	(Tripodi *et al*., 2005; Klein *et al*., 1980)
S. equinus			(Leonardo *et al*., 1999; Schlegel *et al*., 2000)
S. infantarius			(Chadfield *et al*., 2007)
S. gallolyticus			(Van't *et al*., 2005; Ellmerich *et al*., 2000)
S. lutetiensis			(Gavin *et al*., 2003)
S. macedonicus			(Teng *et al*., 2001)
S. pasteuriana			(Galpérine *et al*., 2007)
S. canis	Group G	Urinary tract infection, soft tissue infection, septicemia, bacteremia, pneumonia, and bone infection,	(Facklam *et al*., 1995)
S. porcinus	Groups E, P, U, and V	Urogenital infections, pregnancy complications, and wound infection	(Martin *et al*., 2004; Huang *et al*., 2005)
S. suis	None	Pneumonia, meningitis, arthritis, enteritis, sepsis, endocarditis, deafness, and toxic shock syndrome	(Lau *et al*., 2006)
S. iniae	None	Bacteremic cellulites, arthritis, endocarditis, and bacteremic osteomyelitis	(Finkelstein *et al*., 2003)
S. acidominimus	None	Endocarditis, meningitis, pericarditis, abscess, and pneumonia	(Balm *et al*., 2006)
S. gallinaceus	*None*	*Bacteremia*	(Brouwer *et al*., 2016)

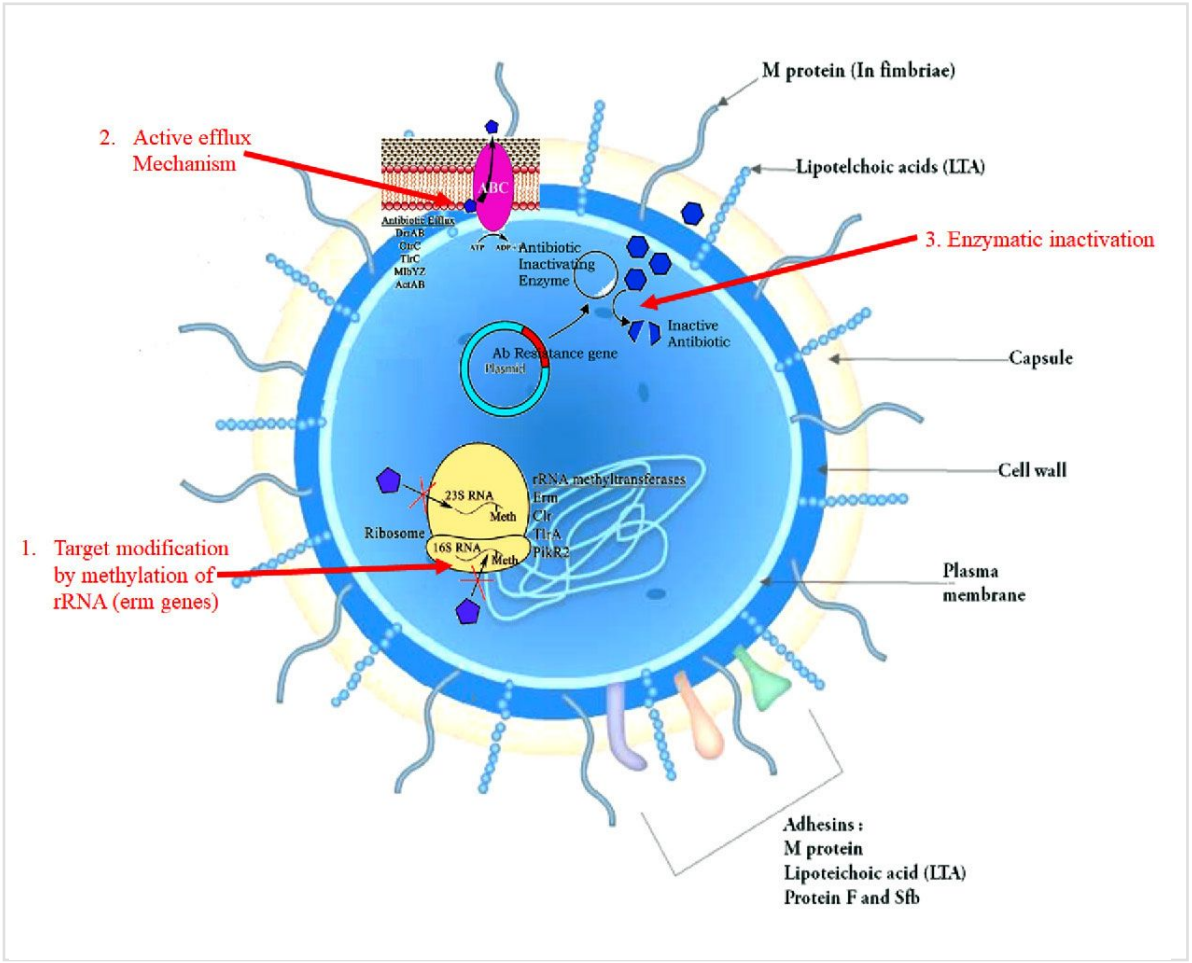

Figure 2. Possible mechanisms of resistance in *Streptococcus* species.

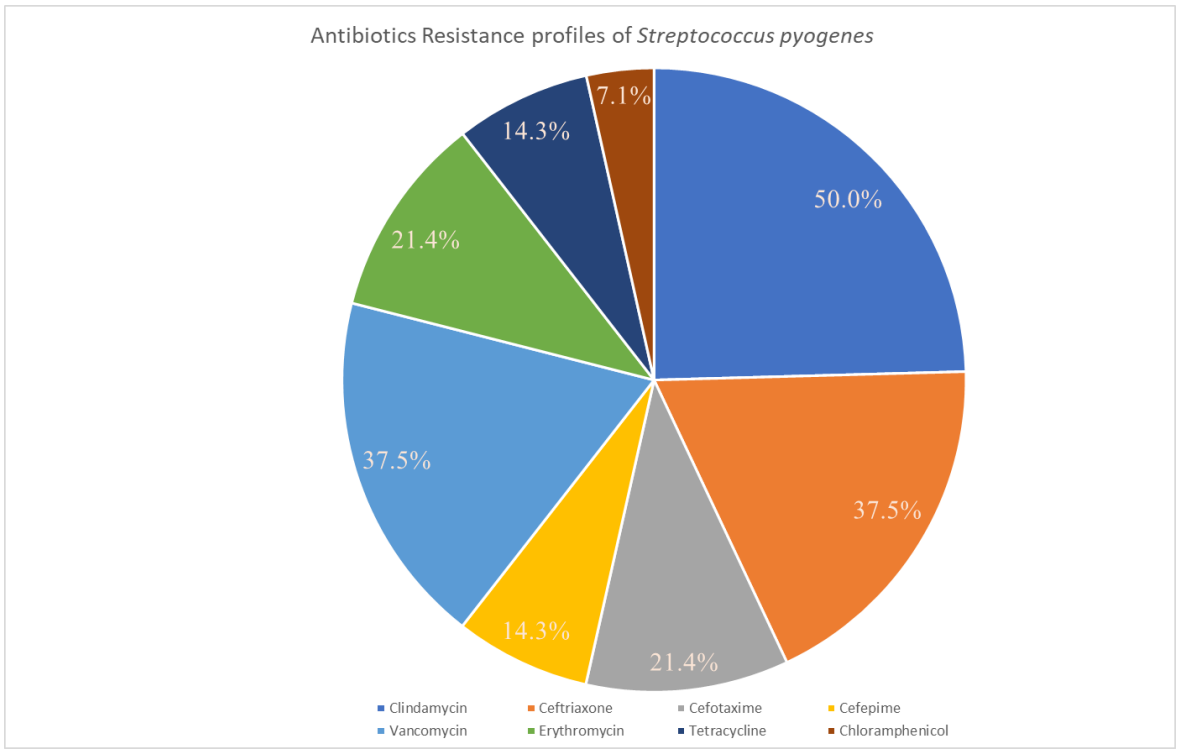

Figure 3. Graphical representation of antibiotics resistance profiles of *Streptococcus pyogenes*.

tract infections, namely sinusitis, pneumonias, and otitis media (Mulholland, 1999). Worldwide, pneumococcal infections account for 1–2 million casualties yearly in both extremes of time (Collignon *et al*., 1996). Once it was believed to be a most susceptible bacteria to standard antibiotics, especially to penicillin. Nevertheless, with the identification of the initial clinically important penicillin-resistant pneumococcus (PRP) appearing in 1967, various investigations from various regions of the globe have registered an elevated occurrence of PRP infections (Lalitha *et al*., 2002). Presently, along with the resistant strains of *S. pneumoniae* to the β-lactam group of antibiotics, there is a remarkable emergence of multidrug-resistant strains (Thomas *et al*., 1999).

Streptococcus pneumoniae can produce invasive disorders like meningitis and bacteremia in addition to respiratory infections. The prevalence of invasive pneumococcal disease (IPD) varies greatly by nation; the CDC stated in 2016 that 90% of IPD in the United States occurred in adults, but the WHO estimates that 75% of IPD occurs in children below the age of 2. Pneumococcal bacteremia is a common consequence of pneumococcal pneumonia, occurring in 25%–30% of adult cases and 12–16% of IPD in children. Since the widespread adoption of the *H. influenzae* type vaccination reduced Hib invasive illness, pneumococcal meningitis has become the most frequent kind of meningitis in children (Golden *et al*., 2019).

There are now 97 different capsular forms of *S. pneumoniae* having a capsule is required for *S. pneumoniae* to survive in the bloodstream and is linked to its potential to produce invasive illness. The presence of the capsule lowers bacterial entrapment in mucus, allowing for easier invasion and inhibiting complement activity and phagocytosis. *Streptococcus pneumoniae* is a highly adaptable pathogen that is prone to genetic recombination as a result of frequent environmental stressors like antibiotic usage. IPD episodes are frequently transitory, with fast and direct therapy; as a result, the organism has little opportunity to adjust to antimicrobial pressure. Pneumococcal carriage, on the other hand, is typically long-term. Carriage serotypes are exposed to extended antimicrobial pressure as a result of their long residence of the nasopharynx, which can lead to the selection of antimicrobial-resistant strains. The frequency of serotype isolation from the nasopharynx, the duration of carriage, and the possibility of antibiotic resistance have all been linked in studies (Straume *et al*., 2015).

Considering India, there are just a small number of findings which demonstrates the resistance pattern in *S. pneumoniae*. Kanungo *et al*.'s (2001) investigations to recognize the resistance patterns of *S. pneumoniae* strains have observed the upsurgence of intermediary sensitivity from Christian Medical College, Vellore, South India. However, research conducted by Goyal *et al*. (2007) in North India indicated 2.3% resistance. A similar investigation from South India has described low-altitude resistance, even though they did not find any strain exhibiting absolute resistance (Farley *et al*., 2001). However, one more cooperative research from 8 Asian nations together with India has shown 35.1% of the total resistance in strains of *S. pneumoniae* (Chawla *et al*., 2010). Table 2 presents the antibiotic resistance patterns of *S. pneumoniae* from various studies conducted at different geographical location over the time.

GROUP B: Group B *Streptococcus*, also known as β-hemolytic *S. agalactiae*, is a pathogenic bacterium that causes infections such as pneumonia, meningitis, and sepsis in pregnant women and newborns (Johri *et al*., 2006); more recently, the infective status of these strains in immunocompromised and elderly patients has been re-evaluated (Le Doare *et al*., 2017).

Resistance patterns of *S. agalactiae*

Two sets of antimicrobial drugs, aminopenicillins and penicillin, are suggested as first choice of treatment against Group B *Streptococcus* infections; whereas Lincosamide (Clindamycin) and macrolides (Erythromycin) correspond to the second choice of antibiotics which are commonly recommended for the patients who are allergic to β-lactams antibiotics. Penicillin G (PEN) is the medicine of first option and is widely utilized in the dealing and stoppage of Group B *Streptococcus* infections, like intrapartum antimicrobial prophylaxis in pregnant women to avoid early inception of Group B *Streptococcus* infections (Orand, 2012). β-lactams and penicillin G are also the most used drug of choice in households, agricultural animals, and aquaculture for preventive or infection management purposes (Simoni *et al*., 2018). Accordingly, penicillin nonsusceptibility (PEN-NS) is a significant burden and could involve alternatives in medication guidelines. Group B *Streptococcus*-associated multidrug resistance, including fluoroquinolone resistance, was identified owing to the outflow mutations or mechanisms in the quinolone resistance determining genes. DNA gyrase (gyrA/gyrB) and topoisomerase IV (parC/parE) are two types of II topoisomerase enzymes (Wessman, 1986).

GROUP D: The strains of *Streptococcus* in Group D were categorized in two varying types in the early 1980s: i.e., *Streptococcus faecium and Streptococcus faecalis*. Later, they were retitled as *E. faecium* and *Enterococcus faecalis*. Ever after that, various new strains have been listed in the *Enterococcus* genus (Facklam *et al*., 1995).

GROUP E: According to Lancefield's classification, the strains of Group E *Streptococcus*, namely *S. porcinus*, is normally associated with pneumonia, sepsis, lymphadenitis, and endocarditis in swine. Around 87 types of infections caused by *S.*

Table 2. Resistance patterns of *S. pneumoniae.*

Study / year	Percentage of resistance to various antibiotics					
	Erythromycin	Penicillin	Cefotaxime	Ciprofloxacin	Cotrimoxazole	Tetracycline
South Indian / 2010 (Chawla *et al*., 2010)	14	4	0	14	24	24
South Indian / 1995 (Facklam *et al*., 1995)	-	4.6	-	-	-	-
South Indian / 1996–2000 (Kanungo *et al*., 2001)	4.6	7.1	-	-	36	12.6
North Indian / 1999–2002 (Goyal *et al*., 2007)	-	18.3	1.7	-	61.7	76.7
Eight Asian countries / 2002–2004 (Orand, 2012)	56.1	35.1	7	0	-	-

Table 3. Resistance patterns shown by the viridans group *Streptococci* (Angeletti *et al*., 2015; Chun *et al*., 2016 ; Woo *et al*., 2004).

Antibiotics	Percentage (%) of resistance							
	Overall % of All Strains	*Various streptococcus species*						
		S. mitis (*n* = 589)	*S. anginosus* (*n* = 290)	*S.sanguinis* (*n* = 179)	*S.salivarius* (*n* = 57)	*S.bovis* (*n* = 11)	*S mutans* (*n* = 7)	Unclassified (*n* = 315)
Penicillin	11.3	20.9	1.7	5.0	8.8	0	28.6	5.8
Ampicillin	13.1	22.7	3.1	8.9	7.3	0	14.3	7.3
Cefotaxime	11.2	19.1	2.1	7.3	8.8	0	42.9	7.3
Ceftriaxone	11.2	19.1	2.1	7.3	8.8	0	42.9	7.3
Clindamycin	36.9	21.7	12.3	15.2	10.5	45.5	14.3	12.9
Erythromycin	36.9	54.8	14.2	36.5	31.6	45.5	42.9	26.3
Levofloxacin	5.1	6.6	1.4	2.3	1.7	18.1	0	7.4
Tetracycline	43.3	42.6	50.9	50.3	17.5	81.8	42.9	36.9

n—total number of strains isolated / studied.

porcinus have also reported in human beings also (Le Bouguenec *et al*., 1990).

Resistance patterns in *S. porcinus:*

An indication which strengthens the role of *S. porcinus* as a recently evolving pathogenic microbe is correlated with the reality that this pathogen has only been inaccessible from mankind in the last two decades. The elevated incidence of Tetracycline resistance among *S. porcinus* bacteria may be associated with the existence of conventional genetic factors in chromosomal DNA of these bacteria, for example, transposons Tn3701 and Tn916, which code for resistance to Tetracycline are extensively spread among other members of the *Streptococcus* genus (Jonsson *et al*., 1991).

GROUPS C AND G: As per Lancefield's classification, *Streptococcus dysgalactiae* subsp. *dysgalactiae* goes to Group C and G *Streptococcus* and shows a key position in mastitis (Rojo *et al*., 2021). Based on unusual instances, this strain was reported in humans and in fish necrotic tissues, as being accountable for several infections. The strain *S. dysgalactiae* subsp. *Equisimilis* from the same group is a β-hemolytic microbe responsible for STSS and sepsis infections in humans.

Resistance patterns *S. dysgalactiae*

Streptococcus dysgalactiae caused diseases in older people who had malignancy or diabetes. The percentage of bacteremia and the number of deaths were slightly higher. Various M-protein genes in the emm or emm-ST sequences were associated with either bacteremia or both Lincosamide and macrolide resistance. Resistance levels to the groups of this group and tetracycline were analogous, but the dissemination of antibiotic resistance strains differed, representing distinct resistance mechanisms. Consequently, there were variations in the epidemiological results, clinical data, and antibiotic resistance genotypes between different regions (Goyette *et al*., 2014).

GROUP R: The *Streptococcus suis* belonging to Group R is accountable for STSS and meningitis. It is a perfectly zoonotic strain, and in fact, human beings nearby swine and/ or consuming swine derived food are a cause for *Streptococcus suis* infections (Segura *et al*., 2016). The antimicrobial resistant patterns of various species of viridans groups of *Streptococci* group are presented in Table 3, in which the first column lists the various antibiotics, whereas the second column shows the overall resistance percentage of all the strains together. This table clearly indicates that these viridans groups got high resistance to antimicrobials like tetracycline, clindamycin, and erythromycin in comparison with other antibiotics (Chun *et al*., 2015).

CONCLUSION

Undiscriminating usage of antimicrobial substances at an unsuitable dosage might be the probable cause of resistance. Consequently, there should be restrictions for the indiscrete use of antimicrobial agents to reduce the development of resistant microorganisms. The development of drug-resistant species and the MDR strains of *Streptococcus* species require uninterrupted national and international monitoring of susceptibility, to develop the best line of treatment. Antimicrobial drug resistance among *Streptococcus* species arising from earlier sensitive inhabitants resulted in parallel gene transfer or point mutations in chromosomes due to the unnecessary use of antibiotics. The strains of *Streptococcus* were recognized as producers of biofilm. The intensified resistance to antibiotics by biofilms among *Streptococcus* species promotes frequent infections, which comprise roughly 80% of microbial diseases in people. The antibiotic resistance in *Streptococcus* species has become the major problem of worry that is categorized and prioritized by the WHO.

These statistics indicate the significance of clinical studies in various geographical regions before recommending certain antimicrobial drugs to various infections to minimize the resistant strains among *Streptococcus* species. An entirely distinct problem is how to slow down the resistance of antimicrobial drugs by these *Streptococcus* species among adolescent children and older persons in long-term care facilities. Answers may include decreasing antibiotic utilization, which is the most important driver of recently gained resistance. Constant observation to measure *streptococcal* resistance is additionally required to identify the occurrence of new strains showing high-level penicillin resistance and more drug resistance. Furthermore, everyone should clearly recognize the scientific importance and influence of antimicrobial drug resistance on streptococcal infections as there is no constantly clear relationship between resistance and medication failure.

Attempts to diminish antibiotic utilization should be promoted by knowledge-sharing programs and healthcare guidelines for professionals. The most excellent approach to

prevent *streptococcal* infection is by the application of conjugate vaccinations. Also, it is essential to examine the development of *streptococcal* infections and resistance, concentrating on serotype replacement. Research aiming at the improvement of new vaccine designs must be adopted to avoid emerging resistant strains.

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AUTHORS' CONTRIBUTIONS

All authors contributed significantly to the conception and design, data acquisition, and data analysis and interpretation; participated in the drafting of the article or critically revised it for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. According to the requirements/guidelines of the International Committee of Medical Journal Editors, all authors are entitled to be authors.

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There are no financial or other conflicts of interest reported by the authors in this review work.

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This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

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