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Full Length Research Article

# CHALLENGES OF MULTI DRUG RESISTANT STREPTOCOCCUS PNEUMONIAE AS A FAST DEVELOPING SUPERBUG AND THE WAY FORWARD

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**ABSTRACT**
Multi drug resistant strains of *Streptococcus pneumoniae* are strains that can withstand the therapeutic effects of three or more antibiotics, mostly the first line antibiotics, which include Chloramphenicol, Cotrimoxazole, Streptomycin, Tetracycline, Sulfonamides, Trimethoprim and Ampicillin. This review attempts to highlight various antigenic properties such as; capsule, pili, various pnemococcal enzymes and specific pneumococcal proteins responsible for multi-drug resistance in *Streptococcus pneumoniae*. In addition, this review further highlights the challenges of multi drug resistant *Streptococcus pneumoniae* among developing countries such as Nigeria such as the influence of drug resistance on patients, the influence of drug resistance on pharmaceutical industries, the influence of drug resistance on antimicrobial therapy, the influence of drug resistance on manpower and the influence of drug resistance on government resources; and how these problems can be prevented through measures such as; the production of new antibiotics and vaccines, the acquisition of modern health facilities and techniques for easy detection of multidrug resistant strains and the development of adequate drug storage facilities.

**Keywords** *Streptococcus pneumoniae*, Multidrug resistant *Streptococcus pneumoniae*, Challenges, Nigeria.

## INTRODUCTION

*Streptococcus pneumoniae* (pneumococcus) is a Gram-positive coccus or bacterium that is responsible for majority of community and hospital acquired pneumonia (Fleck, 2016). Usually they are found in pairs of cocci, or diplococci, but they may also occur in short chains or singly. When cultured on blood agar they demonstrate alpha hemolysis and are non-motile organisms (Ballough, 2018). *Streptococcus pneumoniae* is ubiquitous, but frequently colonizes the upper respiratory tract, where it is regarded as a commensal organism in the human respiratory tract, that is, it benefits from the respiratory tract of human body, without harming it (Henriques-Normark and Tuomanen, 2013; Rao,2011). The human upper respiratory tract also regarded as the human nasopharynx, consists of the nose and throat of the human body, which are the only natural reservoirs for *S. pneumoniae* and this bacterium along with viruses are commonly found in a child's nose or throat and about 60% of small children carry pneumococci in the nose asymptomatically (Henriques-Normark and Tuomanen, 2013; Nunes and Sa-Leao, 2005). The rate of colonization of *S. pneumoniae* appears to be seasonal (that is, its occurrence in the human body especially in the nose and throat is seasonal), and it occurs more during the winter (that the cold or harmattan) period of a year. Studies have shown that it can be isolated from 5% to 70% of healthy adults (Musher, 2000) and 20% to 40% of healthy children (Musher, 2000). Most individuals may be carriers of *S. pneumoniae*, without having any knowledge of their carriage status and such carriers are known as asymptomatic carriers. However the rate of asymptomatic carriage varies with age, environment, and the presence of upper respiratory infections. Similarly, in schools, orphanages and military camps the rate of *S.pneumoniae* carriage among the students, residents and service personnel are 27%–60%, 28%–65% and 50%–60% respectively (Robinson *et al.,* 2001) (Fig 1).

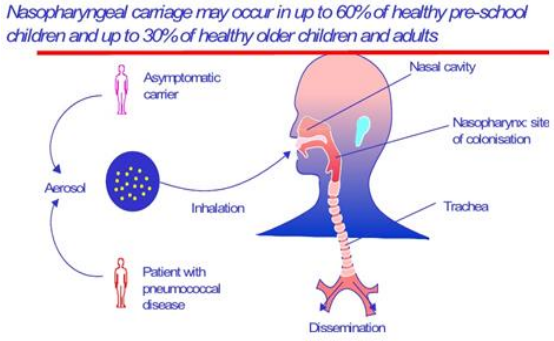


Fig 1: Possible routes that increases the carriage rate of *S.pneumoniae* (Rao, 2011)

Pneumococci are generally transmitted from person-to-person by close contact. Basically, transmission in daycare centers has been demonstrated among infants and toddlers, while in adults, transmission has been shown to be facilitated by crowded living conditions, which is often found in places such as; prisons, military camps, homeless shelters, schools, hospitals, workplace and nursing home (Fleck, 2016). In general, *S. pneumoniae* is basically regarded as the main cause of many acute infections usually referred to as pneumococcal infections in various developing countries, such as Nigeria (Ballough, 2018).

Pneumococcal infections are mainly associated with patients in the hospitals and individuals in the community and can exist as a mild infection and later progress as a severe infection (Rao, 2011). Severe cases of pneumococcal infection mostly lead to deaths, as seen in most developed countries were 20% of pneumococcal septicemia and 30% of both pneumococcal pneumonia and pneumococcal meningitis cause deaths (Tomasz, 1997), such deaths are experienced due to the less attention given to pneumococcal infections when compared to other infections as seen below in Figure 2.

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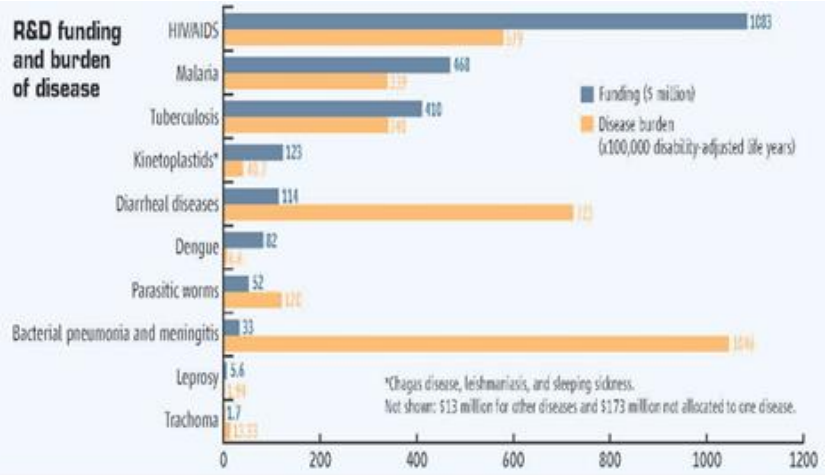


**Fig 2**: Burden of various diseases (Ricciardi, 2010)

**PATHOGENICITY AND PATHOGENESIS OF *S. pneumoniae***

However, infection by pneumococcus only occurs when this pathogen is aspirated into the lungs, it eventually spreads to the blood and traverse the blood-brain barrier to the meninges, once inside the blood it can cause infections throughout the body, such as, pneumonia, bronchitis, otitis media, septicemia, bacteremia and meningitis (Rao,2011). *S. pneumoniae* enter the human body through the nose and mouth and cause infection (Fig 3).

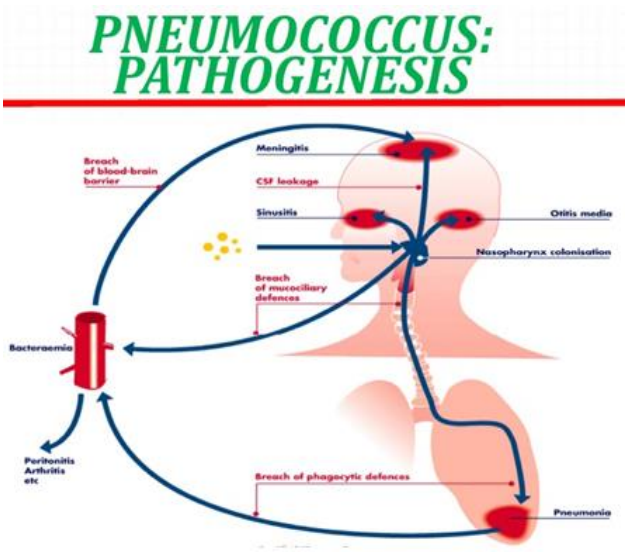


**Fig 3**: Pathogenesis of *S.pneumoniae* (Rao, 2011)

The entrance of this organism into the human body could either be through;

**Direct contact** – Involves the breathing in of infected tiny (aerosol) droplets of fluid that contain the bacteria when launched into the air by infected persons when they cough or sneeze (Fleck, 2016).

**Indirect contact** – Involves the transfer of infected droplets of fluid from an infected hand to a door handle. Which when picked by other individuals, infects them when they touch their nose or mouth (Fleck, 2016).

*S. pneumoniae*, is the most common cause of community-acquired, respiratory-tract infections (such as pneumonia), especially among young children, the elderly, and individuals with certain underlying host defense abnormalities (Center for Disease Control and Prevention (CDC), 2003) and it is also associated with nosocomial-acquired respiratory tract infections. Basically, *S pneumoniae* causes majority of the respiratory tract infections existing worldwide and in most cases, are virulent especially to certain individuals who are; above 65 years, younger than 5 years and immunocompromised (National Health Services, 2017).

Generally, *S. pneumoniae* occurs in two distinct colonies namely: opaque or transparent colony. This particular characteristics, influences the capacity of *S. pneumoniae* to evade host defenses, as well as their virulence. The nasopharynx is usually colonized by the transparent phenotype or colony of *S. pneumoniae* while the opaque type of *S.pneumoniae* usually predominates in the lungs, central nervous system (CNS) and bloodstream infections (National Health Services, 2017). The opaque type of *S. pneumoniae*, unlike its transparent counterpart, has increased capsular polysaccharide and produces more biofilm (Henriques-Normark & Tuomanen, 2013), hence its involvement in many pneumococcal diseases.

**CLINICAL MANIFESTATION OF PNEUMOCOCCAL INFECTION**

Pneumococcal infections are basically of two types namely:

**Non-invasive pneumococcal infections** – these occur outside the major organs or outside the blood and tend to be less serious. Basically it includes: bronchitis (infection of the bronchi (and these are the tubes that run from the windpipe down into the lungs); otitis media (ear infection or middle ear infection); sinusitis (infection of the sinuses) (National Health Services, 2017).

**Invasive pneumococcal infections** – these occur inside a major organ or inside the blood and tend to be more serious and it generally includes: bacteraemia (a relatively mild infection of the blood); septicaemia (a more serious blood infection); osteomyelitis (infection of the bone); septic arthritis (infection of a joint); pneumonia (infection of the lungs); meningitis (infection of the meninges (which is the protective membranes surrounding the brain and spinal cord) (National Health Services, 2017).

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*S.pneumoniae* is also associated with multiple infectious diseases, which is basically categorized into common and less common pneumococcal infections. Common pneumococcal infections include; Respiratory tract diseases (such as; Otitis media, Sinusitis, Tracheobronchitis, Pneumonia and Empyema), Meningitis, Bacteremia/ Septicemia and Peritonitis while less common pneumococcal infections include; Pericarditis, Endocarditis, Osteomyelitis, Septic arthritis, Epidural abscess, Brain abscess and Skin and soft tissue infection (Ballough, 2018;Rao, 2011).

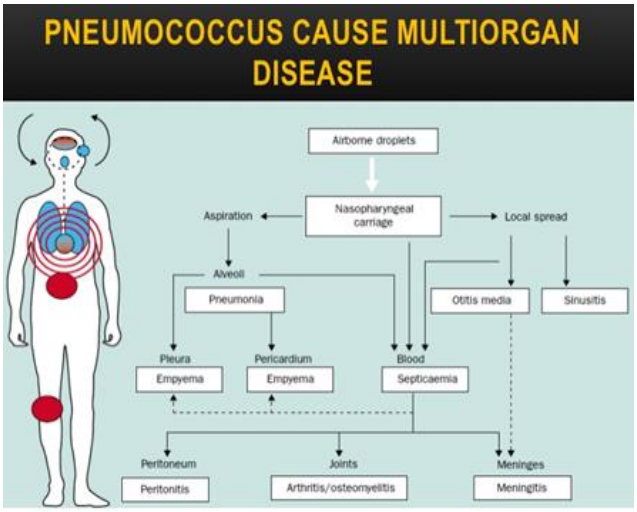


**Fig 4**: Diseases associated with pneumococci (Rao, 2011)

Symptoms of pneumococcal infections are usually said to vary depending on the type of infection present in an individual, but common symptoms associated with pneumococcal infection include sudden: chill, head ache, fever, cough, pleuritic pain, or sputum with a red/brown rusty color (Fleck, 2016; Rao, 2011).

**ANTIGENIC PROPERTIES OF ASSOCIATED WITH *S. pneumoniae***

There are various virulence factors that enhance *S. pneumoniae* to establish a disease in a host, and they are as follows:

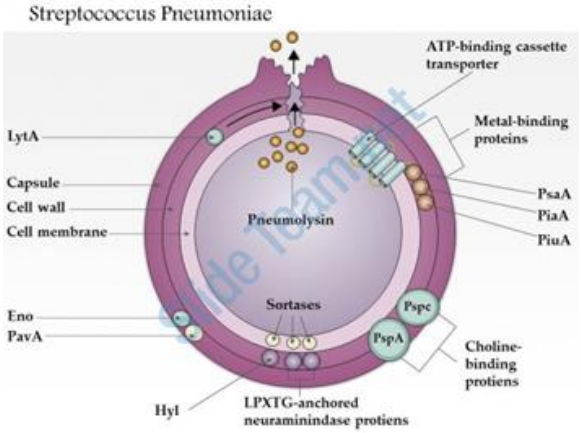


**Figure 5**: Various Proteins associated with the virulence of *S.pneumoniae* (Ricciardi, 2010)

**Capsule**

The capsule of *S. pneumoniae* also referred to as, polysaccharide capsule is basically the outer layer surrounding the cell wall of the pneumococcus. The capsule is one of major virulence factors of the pneumococci, and it is made up of polysaccharides; hence its name, polysaccharide capsule. Pneumococci capsule confers protection against phagocytosis and also inhibits complement activation by the alternative pathway (Hyams, Camberlein, Cohen, Bax and Brown, 2010). The capsules of different pneumococcal serotypes are usually said to resist phagocytosis in various capacities and this is due to the biological properties of the capsular polysaccharide (Magee and Yother, 2001).

**Pili**

Pilus was recently reported among *S. pneumoniae* for the first time (Barocchi, Ries, Zogaj, Hemsley, Albiger, Kanth, Dahlberg, Fernebro, Moschioni, Masignani, Hultenby, Taddei, Beiter, Wartha, Von Euler, Covacci, Holden, Normark, Rappuoli and Henriques-Normark, 2006). Pneumococcal pilus is encoded by the *rlrA* islet, and the pilus is said to contain three pilus subunit proteins, namely; *RrgA*, *RrgB* and *RrgC*. Experimental evidence indicate that this pilus play an important role in the adhesion of the organism to humans, and is mediated mainly by *RrgA* (Barocchi *et al.,*2006). The pneumococcal *rlrA* islet is known to occur in about 30% of clinical isolates (Bagnoli *et al.,* 2008; Barocchi *et al.,* 2006). Similarly, another type of pneumococcal pilus (islet 2) was recently reported (Bagnoli, Moschioni, Donati, Dimitrovska, Ferlenghi, Facciotti, Muzzi, Giusti, Emolo, Sinisi, Hilleringmann, Pansegrau, Censini, Rappuoli, Covacci, Masignani and Barocchi, 2008). Basically, this pilus has three structural proteins and has also been shown to be important for pneumococcal adherence to various cells of the host (Bagnoli *et al.,* 2008) .The distribution of islet 2 in pneumcocci appear to be different from that of islet 1 (*rlrA*) as islet 2 occurs in some clones that lack islet 1 (Moschioni, Donati, Muzzi, Masignani, Censini, Hanage, Bishop, Reis, Normark, Henriques-Normark, Covacci, Rappuoli and Barocchi, 2008).

**Hyaluronidase**

Hyaluronidase is one of the virulence factors and it is regarded as a pneumococcal enzyme, which is basically proteinous in nature. Hyaluronidase occurs more in pneumococcal strains isolated from human meningitis and meningoencephalitis than strains isolated from cases of otitis media (Donkor and Badoe, 2014).The hyaluronidase produced by *S. pneumoniae* plays an important role in causing human pneumococcal meningitis or invasive disease. For *S. pneumoniae* (which produces more hyaluronidase) to cause meningitis or any other pneumococcal invasive disease (PID) in a given host, the hyaluronidase (in a large quantity is needed to) degrade the connective tissues of the host such as the barrier between the blood and the brain (Zwijnenburg, van der Poll, Florquin, van Deventer, Roord and van Furth, 2001), and this thereby facilitate spread or invasion of the bacterium to the brain or other sterile sites namely; blood or lung.

**Pneumococcal Specific Proteins**

*S. pneumoniae* has a vast range of proteins, but only a few actually contribute to the virulence of the organism. The proteins shown to contribute to pneumococcal virulence (pneumolysin, autolysins, neuraminidase, surface protein A, surface protein C, surface adhesion A and IgA protease) (Rao, 2011) are described below:

**Pneumolysin**

Pneumolysin is one of the pneumococcal surface protein and it is a member of the thiol activating haemolysins found in several Gram positive pathogens (Neeleman, Klaassen, Klomberg, de Valk and Mouton, 2004). Basically, this protein contributes to the virulence of *S. pneumoniae*, through diverse mechanisms (or processes) (Ballough, 2018) such as; it

- elicits the production of inflammatory cytokines like tumour necrosis factor alpha.
- inhibits the activity of cilia on human respiratory epithelial cells
- impedes the bactericidal activity and migration of neutrophils
- inhibits lymphocyte multiplication and antibody synthesis.
- activates the classical complement pathway in the absence of anti-toxin antibody (Ballough, 2018; Fleck, 2016)

**Autolysins**

This is also another type of pneumococcal surface protein. *S. pneumoniae* produces three types of autolysins, namely; *LytA*, *LytB*, and *LytC*. The major pneumococcal autolysin, *LytA* has been suggested to play a role in pneumococcal pathogenesis by releasing pneumolysin from the cytoplasm (Donkor and Badoe, 2014). However, *LytB* is highly expressed during exponential growth phase of *S. pneumoniae*, and it is usually used to separate cells, while the use of *LytC* is yet to be confirmed (Donkor and Badoe, 2014).

**Neuraminidase**

Neuraminidase cleaves sialic acid from many host molecules, and when this occurs the host tissues are said to be damaged. Damaged host tissues exposes receptors for pneumococcal adhesins, and this thereby facilitating colonization (that is attachment) and invasion of *S. pneumoniae*. *S. pneumoniae* has three genes encoding for neuraminidases namely, *nan*A, *nan*B, and *nan*C. Pettigrew, Fennie, York, Daniels and Ghaffar, 2006, investigated 342 pneumococcal isolates of different serotypes and sequence types, for the presence of *nan* genes; all the isolates carried the *nan*A gene; a majority carried the *nan*B gene, while about 50% of the isolates carried the *nan*C gene.

**Pneumococcal Surface Protein A (PspA)**

*PspA* is also one of the pneumococcal surface proteins; it acts as a specific receptor for lactoferrin, and it also helps the *S. pneumoniae* to acquire iron from host cells (Donkor and Badoe, 2014). Mutagenesis studies have shown that *PspA* inhibits activation of the complement component C3 and thereby inhibits the complement cascade (Donkor and Badoe, 2014).This interference with complement activation serves to facilitate pneumococcal survival and host invasion

**Pneumococcal Surface Protein C (PspC)**

*PspC* has some structural similarity with *PspA* and can cross-react with *PspA* (Donkor and Badoe, 2014). *PspC* binds to the polymeric immunoglobin receptor that normally binds secretory IgA (Donkor and Badoe, 2014). This binding enables translocation of *S. pneumoniae* across the respiratory epithelium. *PspC* also binds factor H which hinders the formation of C3b as well as activation of complement (Donkor and Badoe, 2014).

**Pneumococcal Surface Adhesin A (PsaA)**

PsaA is a component of an ABC-type manganese permease membrane transport system and has amino acid similarity to lipoprotein adhesins in some viridan streptococci (Donkor and Badoe, 2014). *PsaA* and three other genes, *psaB*, *psaC*, and *psaD* form the *psa* operon. PsaA mutants in most cases are said to express decreased adherence of pneumococci to mammalian cells (Anderton *et al.,* 2007).This observation has been attributed to the effect of lower expression of other adhesions as a result of loss of manganese transport. Evidence in support of this is the fact that when other genes of the same operon are mutated similar loss of adherence is observed (Donkor and Badoe, 2014).

**Pneumococcal Surface Adherence and Virulence Factor A (PavA)**

*Pav*A is located on the outer surface of *S. Pneumoniae,* though it lacks the classical cell wall determinants (Donkor and Badoe, 2014). *Pav*A has been demonstrated to be important in pneumococcal virulence, without direct involvement in host cell interactions and inflammatory responses. *Pav*A binds to fibronectin and regulates other virulence determinants of *S. pneumoniae* that are important in adherence and survival of the organism *in vivo* (Donkor and Badoe, 2014).

**Others Virulence Determinants**

Apart from the virulence determinants described in this section, there are several other pneumococcal virulence determinants, such as beta-galactosidase and enolase (Terra, Homer, Rao, Andrew and Yesilkaya, 2010).

However, based on the occurrence of these virulent or antigenic properties possessed by *S.pneumoniae*, many *S.pneumoniae* are said to initiate pneumococcal infections which are said to withstand the effect of many existing antimicrobials; thereby remaining viable and/or multiplying in the presence of these antimicrobials (Oyedum, 2015; Neu, 1992). Basically, antimicrobial resistance of *S.pneumoniae,* is regarded as a serious threat to public health. The percentages of antibiotic resistance (AR), especially multidrug resistance (MDR), has continued to increase in developed and developing countries, and this leads to high healthcare costs, failed treatments, prolonged stay in the hospitals, increased disease and deaths (Magiorakos, Srinivasan and Carey, 2012). Prior to the development of antibiotic resistant pneumococci, *S. pneumoniae* was almost uniformly susceptible to penicillin and other narrow-spectrum cephalosporins, erythromycin, macrolides and vancomycin, but since 1960s, resistance to penicillin and other antimicrobial agents has spread rapidly and was first reported in Australia in 1967, in New Guinea in 1969, in South Africa in 1977 (Appelbaum *et al.,* 1977; Jacob *et al.,* 1978), and in many other countries throughout Africa, Asia and Europe.

Antibiotic resistant pneumococci, originally called penicillin-resistant pneumococci (PRP) appeared to have acquired genetic material that encoded resistance to penicillin as well as to other multiple classes of drugs commonly used, such as trimethoprim-sulfamethoxazole, macrolides, and fluoroquinolones (which began to appear in the late 1990s), hence the development of multi drug resistant *Streptococcus pneumoniae* (MDRSP); which is said to be resistant to three or more classes of antibiotics, was said to develop during 1990s (Musher, 2017). MDRSP is a real concern because it is difficult to eradicate and carries a higher risk of causing complications.

However, the major factor in the emergence and spread of antibiotic-resistant strains or multidrug resistant strains of *S. pneumoniae* is basically the misuse of antibiotics by individuals or

patients, which in turn exerts selective pressure on certain strains of *S. pneumoniae,* and this is said to lead to the development and prevalence of resistant *S. pneumoniae* (Diekema, Brueggemann and Doern, 2000).

**MECHANISMS OF RESISTANCE OF *S. PNEUMONIAE***

**Penicillin and β-lactam resistance**

Generally, *S. pneumoniae* exhibit penicillin resistance by altering their penicillin binding proteins (PBPs) on their cell wall, hence a decreased affinity for penicillin, is said to occur (Cornick and Bentley, 2012). PBPs are membrane-bound proteins or enzymes found on the cell walls of pneumococci. The PBPs usually enhances the attachment of the pneumococci to any surface, but once antibiotics are involved, the pneumococci is said to alternate its binding sites susceptible to the available antibiotic.

There are six PBPs namely; PBP1a, PBP1b, PBP2x, PBP2a, PBP2b and PBP3, usually found to occur on the cell walls of pneumococci (Donkor and Badoe, 2014; Song, 2013). However, alterations are said to occur in four PBPs namely; PBP1a, PBP2b, PBP2x and PBP2a. These alterations in PBPs that result to penicillin resistance, is usually caused by mutations in *pbp* genes (Song, 2013). Such mutations usually arise due to intra species gene transfer (that is, gene transfer within the same species) or interspecies gene transfer (that is, gene transfer within different species). In most cases interspecies gene transfer, usually occurs between *S. pneumoniae* and commensal *Streptococcus* species such as *S. mitis* and *S. oralis*, which results in a mosaic gene sequence of *pbp* in *S. pneumoniae* (Zapun, Contreras-Martel and Vernet, 2008). Similarly pneumococci resistant to penicillin are also said to be resistant to other beta-lactam drugs such as cephalosporins such as ceftriaxone and cefotaxime (Weber and Rutala, 2018).

**Macrolides resistance**

*S. pneumoniae* exhibit various mechanisms of macrolide resistance. The commonest mechanism of macrolide resistance carried out by *S. pneumoniae*, is the methylation of the 23S ribosomal target site (that is, the introduction of a methyl group to the 23S ribosomal target site) (Song, 2013). Which is usually encoded by the *ermB* gene, and this type of resistance to macrolides, is said to be a high-level resistance. The other mechanism of macrolide resistance exhibited by *S. pneumoniae*, is the efflux pump, which is usually encoded by the *mef* genes (namely; *mefA* and *mefE*) and this type of resistance, is said to be a low-level resistance (Wierzbowski, Swedlo and Boyd, 2005).
The *mefA* gene which mediated low-level resistance was the most common type of macrolide resistance in the United States (Shortridge, Doern, Brueggemann, Beyer and Flamm, 1999), while *ermB* gene which mediates high-level resistance is more common type in Africa and European countries such as; South Africa and Asian countries (Felmingham, Canton and Jenkins, 2007). But, recently in the United States, *ermB* gene which mediates high resistance has been observed and it is gradually increasing. This therefore, results to a situation, whereby there is an equal prevalence of resistance from *mefA* and *ermB* (Jenkins and Farrell, 2009) In most Asian countries, *ermB* was found in >50% of pneumococcal isolates either alone or in combination with *mefA* (Kim *et al.,* 2012).

**Fluoroquinolones resistance**

Pneumococcal resistance to fluoroquinolones is usually mediated by (spontaneous point) mutations in the quinolone resistance determinant region of *gyrA* and/or *parC* (Cornick *et al*., 2012).The preferential target site, for most fluoroquinolones such as ciprofloxacin and levofloxacin in *S. pneumoniae* is the gene *parC,* which inhibits topoisomerase IV while the target site for fluoroquinolones such as moxifloxacin (Li, Zhao, and Drlica, 2002) is the gene known as *gyrA*, which inhibits DNA gyrase. However, pneumococci isolates develop resistance to ciprofloxacin when mutation, which alters (ciprofloxacin's) target sites on the gene named- *parC* occurs. The resistance of pneumococci isolates to ciprofloxacin, thereby makes such isolates susceptible to the newer fluoroquinolones such as levofloxacin, gatifloxacin, moxifloxacin and gemifloxacin, while high-level fluoroquinolone-resistant strains typically have dual mutations affecting both *parC* and *gyrA* (Balsalobre and De La Campa, 2008).

**Epidemiology of multi drug resistant *Streptococcus pneumoniae* in the 21st Century**

The treatment of *S pneumoniae* continues to be a challenge in the 21st century, especially as the increasing resistance of *S pneumoniae* to a variety of antimicrobial agents such as penicillins, cephalosporins, macrolides, and quinolones is said to develop. Currently, up to 40% of clinical infections are caused by a pneumococcal strain resistant to at least 1 drug and 15% are due to a strain resistant to 3 or more drug (Gillespie, McHugh, Hughes, Dickens, Kyi and Kelsey, 1997).
Resistance to cephalosporins such as; cefotaxime and ceftriaxone in *S. pneumoniae* remains relatively infrequent worldwide, although resistance to cefuroxime has been reported to be much higher. The rates of nonsusceptibility to cefotaxime in *S. pneumoniae* isolates in adults varied from 5.1 to 11.1%, while the rates of nonsusceptibility to cefuroxime varied from 17.7 to 43.9% in 8 European countries between 2001–2003 (Pfaller, Ehrhardt and Jones, 2001). According to the SENTRY Antimicrobial Surveillance Program in the United States, the rate of nonsusceptibility to ceftriaxone in pneumococci has increased from 3% in 1998 to 11.7% in 2011(Jones *et al.,* 2013). According to the ANSORP surveillance study, non-susceptibility rates to cefuroxime were relatively high in 2008–2009, particularly in Korea (73.7%), Vietnam (71.7%), Taiwan (65.8%) and China (65.1%) (Kim *et al.,* 2012).

**Challenges of Multi Drug Resistant *Streptococcus Pneumoniae* in Nigeria**

In developing countries especially Nigeria, each challenging factor such as, high infectious disease burden, rampant poverty and deprivation, the emergence of antimicrobial resistance in the community and hospitals, makes millennium development goals quite unattainable. The implications are manifold: for the Individual, the hospital, and the public health system. For the patient, antimicrobial-resistant infections mean increased morbidity and mortality, financial drain, and emotional trauma to self and dependents. For relatively well patients and hospital personnel, it means colonization and unrecognized sources of spread within the hospital (Zavascki *et al*., 2006) and community. For the hospital administration, it is a clear indicator of poor administration and allocation of funds, poor infection control, nonscientific approach to an essentially scientific problem and poor quality assurance of antibiotics in use. In most cases, when infections become resistant

to first-line antimicrobials, treatment has to be switched to second- or third-line drugs, which are nearly always much more expensive and sometimes more toxic as well, e.g. the drugs needed to treat multidrug-resistant forms of *S. pneumoniae* are over 100 times more expensive than the first-line drugs used to treat non-resistant forms or single drug- resistant forms. In many countries, the high cost of such replacement drugs is prohibitive, with the reason that some diseases can no longer be treated in areas where resistance to first-line drugs is widespread. However, an alarming situation occurring in most developing countries, is basically where resistance is developing for virtually all currently available drugs, thus giving rise to a condition where by antibiotics are inefficient. Even if the pharmaceutical industry were to step up efforts to develop new replacement drugs immediately, current trends suggest that some diseases will have no effective therapies within the next ten years (Zavascki *et al*., 2006).

However, various challenges of multi drug-resistant pathogens affect patient outcomes in different ways: The resistance genes can cause mortality and morbidity; it can also alter the fitness of a bacterial pathogen, making it more or less virulent; the presence of resistance in a bacterial pathogen can lead to a delay in the administration of appropriate antimicrobial therapy (that is delay in treatment); it can also lead to a high cost of treatment and the use of antimicrobial agents that may have adverse effects on health etc.

**The influence of drug resistance on the patients**

Mortality and morbidity are regarded as consequences that occur due to antibiotic resistant organisms. Patients with resistant organisms usually have longer course of disease or fatal outcome (which is mostly, death); moreover, as these patients remain infectious for a longer period, morbidity and transmission of the microorganism are increased. Such increased morbidity was documented in outbreaks of diseases such as pneumococcal infections (Detsky *et al*., 1990). In hospital infections, resistant microorganisms and inappropriate antibiotic therapy increase the risk of colonization, infection, and spread of the resistant organisms (Detsky *et al*., 1990). In addition mortality rate associated with patients have been estimated to be twice as high for patients infected with resistant organisms than for those who were not infected with resistant organisms (Detsky *et al*., 1990).

**The influence of drug resistance on antimicrobial therapy**

Effective treatment of resistant organisms with efficient therapies in most cases, is usually delayed (Lautenbach *et al*., 2001), based on the fact that most available therapeutic agents are less effective on the resistant organisms. Also patients infected with multidrug resistant *S. pneumoniae* strains also have significantly longer hospitalizations and greater hospital charges than other patients.

Infections caused by antimicrobial-resistant organisms also may require the use of certain therapies that can lead to adverse side effects. Most of the toxic therapies used for multi-drug resistant strains could be associated with a high risk of renal dysfunction. Patients infected with organisms that are resistant to all available antimicrobials often require surgical procedures to remove the nidus of infection; patients with infections that are not amenable to surgical debridement have high mortality rates (Lautenbach *et al*., 2001).

**The influence of drug resistance on the pharmaceutical industries**

In most developing countries, such as Nigeria due to increasing conditions of resistance among the populace, the general populace tends to experience scarcity of antimicrobial drugs in poor countries with a high prevalence of infectious diseases this therefore means that, the demand for antimicrobial agents exceeds their supply. This imbalance makes Africa and other developing regions, a counterfeiters' paradise (Okeke *et al.,* 2007). However in the course to satisfy the therapeutic needs of most individuals most pharmaceutical industries and outlets engage in the production and sell of counterfeit drugs, which in turn promotes resistance in a patient.

**The influence of drug resistance on manpower**

One of the challenges of drug resistance is that, it tends to reduce the manpower of the general populace. In areas where resistant strains are prevalent, most patients are subjected to many and different types of antibiotics. This in turn, renders the populace weak and reduces the productivity of such country.

**The influence of drug resistance on government and individual's resources**

In most developing countries like Nigeria, where resistant strains are prevalent, patients find it difficult to procure and consume a complete dose of antibiotics and also to ensure the quality of antimicrobial drug. However in order to eliminate the resistant *S. pneumoniae*, government and individuals are said to utilize twice the resources required to treat non-resistant *S. pneumoniae*.

**Prevention of Multi Drug Resistant *S. Pneumoniae***

Basically fast developing multi drug resistant *S. pneumoniae* can be prevented through various measures such as, better immunization programmes; better diagnostic strategies and intake of balanced nutrition (to boost immune system). In addition, establishment of antibiotic resistance surveillance programmes at various health centres in order to reduce the spread of resistant strains of *S. pneumoniae* should be encouraged. Other related measures for preventing multi drug resistant *S. pneumoniae* include the following:

**Awareness of resistant *S. pneumoniae* to the public**

Health care professionals and the entire public should be sensitized on the fast developing *S. pneumonia* and awareness on the ills associated with inappropriate use of available antibiotics should be promoted by the government in collaboration with the health care authorities to avoid huge investment of time, effort, and large resources required to control antibiotic resistant bacteria.

**Development of New Antibiotics and Vaccines**

This is also one of measures employed to eradicate multi drug resistant *S. pneumonia*e. Basically new antibiotics as well as new pneumococcal conjugate vaccines (containing non vaccines serotype strains of *S. pneumonia*e) are needed to be developed by various life scientists in order to boast the immune response and curtail the already existing resistant strains of *S. pneumoniae*.

**Phage Therapy**

Phage therapy can also be used to deal with antibiotics resistance. This approach had already been used by the Russians during the Second World War. Therapeutically, bacteriophages were used as a prophylaxis against cholera, typhoid fever, and dysentery from

the 1920s to the early 1940s (Rao, 2011; Okeke *et al.,* 2007). The practice was abruptly stopped when synthetic antibiotics were introduced after World War II (Rao, 2011). However, due to the increase in multi-drug-resistant bacteria, bacteriophage therapy once again has become of keen interest. Bacteriophage therapy is quite attractive for the following reasons:

- phage particles are narrow spectrum agents, which means they posses an inherent mechanism to not only infect bacteria but specific strains
- other pathogens may be targeted through manipulation of phage DNA
- exponential growth and natural mutational ability make bacteriophages great candidates for thwarting bacterial resistance

**The Use of Modern Facilities and Techniques**

The wider accessibility of computers and the ability to track antibiotic-resistance genes with molecular techniques have enhanced understanding and tracking of the spread of antibiotic resistant genes. With the appropriate computerized surveillance, a hospital laboratory may be able to detect/ diagnose rapidly the emergence of a new type of resistance or the presence of a new microbial strain within a specific patient population. Hospital administrations in developing countries should also back their Infection Control Committees, through adequate surveillance to curtail hospital infection rates due to resistant strains which may be prevalent in the environment by using techniques such as restriction Endonuclease Digestion Analyses of microbial genomes and genetic probes of antibiotic resistance genes by Polymerase Chain Reaction (PCR) make it possible to confirm the presence of new genes in the environment.

**The provision adequate portable water facilities**

The provision of safe water such as tap water system and boreholes and sanitation to those who cannot afford them and to public institutes such as schools, health centers, and markets is the single most important intervention for preventing outbreaks and sporadic diseases such as pneumococcal infections, usually caused by resistant *S. pneumoniae*. Also the Federal, State and Local Government should treat their water bodies once or twice every week to ensure the supply of adequate water void of resistant strains to the public.

**The enforcement of standard laws to curtail resistance**

Government of developing countries should ensure that in every rural location, there is an establishment of an adequate health care centres. Such provision would in turn prevent the development of unofficial drug outlets, which tend to be source to easy access of antibiotics in a location and thus, encourage the development of antibiotic resistant organisms.

In the same vein, standard procedures should be enforced and implemented among various indigenous pharmaceutical industries to prevent the production of counterfeit drugs. Similarly, such industries should be encouraged to employ adequate storage facilities to maintain the potency and quality of most antibiotics used in Nigeria, to prevent and reduce the development and spread of resistant strains of *S. pneumoniae*.

**Conclusion**

Based on the fact that most children are been administered with adequate doses of vaccines at various intervals, many non-vaccine serotypes (that is, serotypes of *S. pneumoniae*, which were not included in the production of a particular vaccines) are said to develop resistance and infect commonly vaccinated individuals, such as the infants and aged. Hence, the development of resistance by such serotype to the available vaccine and subsequently to the available antibiotics is said to occur and this in turn, possess a great challenge in the treatment of various infections of *S. pneumoniae* It is therefore necessary to create awareness on the prevailing resistant serotypes within a region and the ills associated with them. This will therefore go a long way in providing adequate information to the government and scientists on the various serotypes of resistant *S. pneumoniae*, which will in turn assist in the production of more adequate drugs and vaccines to eliminate them.

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