Antimicrobial Resistance in Syphilis: An Emerging Public Health Crisis

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ABSTRACT

Syphilis, caused by the spirochete bacterium Treponema pallidum, has posed a global public health challenge since the fifteenth century. This chapter provides a comprehensive exploration of the multifaceted nature of syphilis, its historical background, and the emerging threat of antimicrobial resistance (AMR) in its management. A mother infected with syphilis during pregnancy can transmit the disease to her unborn child, and this sexually transmitted infection sy can progress through various stages, each presenting different symptoms and characteristics. The initial focus is on the escalating concern of resistance in syphilis, as it compromises the effectiveness of conventional treatment strategies, particularly the shortage of Benzathine penicillin G reported in some regions. Certain populations, including pregnant women, individuals with HIV, and men who engage in intercourse with males, are particularly at risk due to the increasing prevalence of bacteria that are resistant to penicillin and its replacements, tetracycline and macrolides. To overcome syphilis resistance, a combination of therapies is one of the most effective strategies. While a single antibiotic is frequently used for the duration of syphilis therapy, mixing several antimicrobial medications can improve treatment efficacy and reduce the likelihood that resistance will develop. The synergistic effects of antibiotic combinations such azithromycin, doxycycline, and benzathine penicillin have been researched. This chapter aims to raise awareness about the urgent public health crisis posed by AMR in syphilis. Examining the causes, background, along with mechanisms of syphilis highlights the need for a worldwide strategy to tackle the growing issue of antibiotic resistance. In order to create effective strategies to stop the dissemination of resistant strains, give appropriate care, and lessen the public health burden of syphilis, it is essential to understand the many aspects of antimicrobial resistance (AMR) in syphilis.

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1. INTRODUCTION

Syphilis is a sexually transmitted infection caused by the spirochete bacterium Treponema pallidum. (Carbone et al. 2016) It has a lengthy history that dates to the fifteenth century and continues to be a global public health issue. A mother who has the virus during pregnancy can pass it on to her unborn child through sexual intercourse. There are different phases of syphilis, and if ignored, it can have a serious negative impact on health (Wasserman et al. 2007). Treponema are members of the Spirochaetaceae family. Many Treponema species are part of the microbiota of animals and humans. Spirochaetes are opportunistic bacteria that are associated with human gingivitis and chronic periodontitis. The most important species of Treponema is the Treponema pallidum, which is a causative agent of syphilis. Syphilis is a chronic, multi-stage infectious disease (Stamm 2015). Syphilis progresses through different stages; each has its own Symptoms and characteristics.

In Primary Syphilis, single painless lesions occur usually but can be multiple and painful later on (Ward et al. 2007). The chancre appears 3 Weeks after infection and lasts for 3 to 8 weeks and heals. regardless of whether a person receives treatment (Pagani et al. 2021). After primary syphilis, Secondary syphilis occurs between 4 to 8 weeks. Symptoms include rashes, mucosal lesions, and sores in the mouth, vagina and anus. Rashes are mainly papular and rarely papules ulcerate and can be associated with mucosal ulceration. Condylomata lata (wart like lesions) may develop in the moist areas like the mouth and groin region. Symptoms may also include fever malaise, headache, swollen lymph and neurological problems (Ward et al. 2007). Without treatment secondary syphilis becomes latent and non-infectious, there are no sign and Symptoms show and deteriorate changes may occur in early latent disease (the two years of latency) but less in late latent disease (Nyatsanza and Tipple 2016).

T. ertiary syphilis can appear typically 15 to 30 years after onset of infection. It is rare, and can affect any tissue (granulomatous), cardiovascular system. nervous system and mainly skin and boner affected. (Nyatsanza and Tipple 2016). Antimicrobial resistance (AMR) is the term used to describe a microorganism's capacity to resist the effects of antimicrobial medications, which can result in treatment failures and the spread of resistant strains. Antimicrobial resistance in syphilis has become a growing source of worry in recent years. This resistance can limit the efficacy of conventional treatment plans and make illness management and control more difficult. Because vaccine is not available for syphilis. So antibiotics is the main component for control. Benzathine penicillin G is used for the early syphilis. Shortage reported in this antibiotic in France so there is a need alternative treatment (Sanchez et al. 2020). Syphilis has become a public health problem in vulnerable population due to mutation in antibiotic resistance. In Vulnerable population (such as men who have sex with men, HIV patients and pregnant women) antimicrobial resistance is emerging in macrolides and tetracycline. These medicines use as alternate treatment for syphilis in those patients allergic to penicillin. So, there is a need to focus on macrolide and tetracycline resistance (Orbe-Orihuela et al. 2022b). This chapter's goal is to give readers a thorough grasp of the rising public health concern known as antibiotic resistance in syphilis. It aims to investigate the causes, spread, and historical context of syphilis, as well as the mechanisms. The overall goal of this chapter is to raise awareness of the danger that syphilis poses due to antibiotic resistance and to stress the necessity of tackling this problem globally. Understanding the different facets of antimicrobial resistance in syphilis can help us create efficient plans to stop the spread of resistant strains, provide proper care, and ultimately lessen the impact of syphilis on the general public's health.

2. UNDERSTANDING SYPHILIS

2.1. HISTORICAL BACKGROUND OF SYPHILIS

Treponema pallidum is the bacteria that causes the sexually transmitted disease syphilis. Its history dates back centuries, with the earliest recorded outbreaks occuring in Europe in the late 15th century. There were many possibilities in the time before 15th century where syphilis would have been discovered but they were not fully supportive in account of proof (Rothschild 2005). Girolamo Frasastoro came up with the term "syphilis sive morbus gallicus" in 1530. The phrase "great pox" emerged as a way to distinguish the illness from smallpox due to the associated rash (pox). Despite the two centuries of usage for the phrase, syphilis grew to be a cultural disgrace, leading to a number of attributions. The Germans and the English referred to it as "the French pox", the Russians and the Poles called it "the Polish sickness", the French called it "the Neapolitan sickness", some Flemish, Dutch, Portuguese, along with North Africans called it "the Spanish sickness" or as "the Castilian sickness", and the Japanese called it "the Canton rash" or as "the Chinese ulcer". In India, Muslims and Hindus both held the other accountable for their actions. In the end, the Europeans were held entirely to blame (Hayden 2003). The phrase "lues venera" (or else "venereal pest") was originally used in a book on the ailment authored in the sixteenth century by the Parisian educator called Jean Fernelius, who work and interests focused primarily in treating the condition using mercury.

2.2. SYPHILIS AND WAR

The French army's conquest of Naples was commonly blamed for the spread of syphilis throughout Europe. Less well-liked hypotheses have, however, been evolved since then (Winspeare 2016). The Edict of Expulsion of the Jews, issued in 1492 by Ferdinand de Aragon and Isabel of Castilla, ordered the expulsion from Spain and the remainder of its lands of all people of Hebrew descent who refused to convert to Catholicism. About 200.000 Jews have currently departed the nation for Northern Africa and Southern Europe. A portion of them briefly settled at Rome's walls while traveling there; they were barred entry, and an outbreak killed 30.000 people in the new Diaspora. After all efforts, the sickness that ultimately came to be known as syphilis makes its way into the ancient city of Rome. As a result, some historians of the time claimed that Jews were to blame for the spread of syphilis in Europe because the illness was already present in Italy before to the French invasion of Naples in 1495(Tampa et al. 2014).

2.3. PATHOGENESIS AND STAGES OF SYPHILIS

2.3.1. SPECIES OF SYPHILIS

The chronic infectious condition known as syphilis is caused via the spirochaete *Treponema pallidum* strains pallidum. The order Spirochaetales, which consists of spiral-shaped pathogenic bacteria, includes the genus *Treponema*. The genera Leptospira and Borrelia are further members of this group. In addition to *T. Pallidum* subspecies pallidum, which causes venereal syphilis, other pathogenic treponemes that affect humans involve *T. Pallidum* subspecies pertenue, which causes yaws, *T. Pallidum* subspecies endemicum, which causes endemic syphilis, and *T. carateum*, which causes pinta (Jaiswal et al. 2020). The so-called 'endemic' treponemes are morphologically identical to each other as well as to *T. Pallidum* subspecies pallidum, have strong antigenic relationships, and exhibit a high degree of DNA similarity. However, they differ in terms of geographic distribution, host tissue specialization, and animal infectivity.(Antal et al. 2002).

2.4. AGENT OF SYPHILIS

Syphilis' causal agent, *Treponema pallidum*, was discovered in 1905. Since then, other pathogenic isolates have been discovered, including the *Truffi*, *Gand, Gent,* and *Ami* strains as well as the Nichols pathogenic isolate. The Nichols pathogenic strain is the one that has received the greatest research attention. It was first isolated from a person with secondary syphilis' cerebrospinal fluid in 1912, and it has since been passed through rabbit testes. It has remained harmful for humans even after 65 years. No pathogenic strain of *T. Pallidum* has been in vitro grown to date, not even this one.(Miao and Fieldsteel 1978). The pathogenesis and stages of syphilis is enlisted in Table 1.

Table 1: Pathogenesis and stages of syphilis**.**

Stages of Syphilis	Symptoms	Time period	Diagnosis	References
Primary	A chancre, painless sore, appears at the infection site, most frequently on or close to the mouth, genitalia, and the abdomen	Usually, 3 to 6 weeks	Delayed diagnosis or remains undetected	(Andersen 1978)
Secondary	One of the most typical symptoms is a non-itchy rash which appears on the soles of the feet, palms of hands, and the backs of the human body. Fever, exhaustion, a sore throat, pains in the muscles, enlarged lymph nodes, and hair loss are further symptoms.	4 to 10 weeks	Delayed Diagnosis	(CHAPEL 1980; Anderson et al. 1989)
Latent	Usually, no symptoms	Months to years	Serological tests	(Stamm 2016c).
Tertiary	Tertiary syphilis symptoms might include dementia, inability to coordinate an individual's movements, paralysis, numbness, and blindness	Several years	Serological Tests	(Singh and Romanowski 1999).

2.5. PATHOGENESIS

T. Pallidum is a helically formed, micro-aerophilic bacterium with a length of 6–20 m long and 0.1-0.18 m in diameter. It is made up of a central protoplasmic cylinder that is encircled by a peptidoglycan layer, the outer membrane, and the cell membrane (Wang 2015). Motility is provided by 2 to 3 flagella that protrude from both ends of the organism. The outer membrane of *T. Pallidum* lacks lipopolysaccharide but does contain a small amount of surface-exposed transmembrane proteins. *T. Pallidum* has been classified as a stealth pathogen due to the absence of immunological targets on the outer membrane. The uncommon membrane proteins of *T. Pallidum* have the potential to be virulence determinants, and at least one of them has been identified as a porin despite the fact that nothing is known about them.(Blanco et al. 1997).

A repeat gene Tpr gene has been identified in recent studies. It has been demonstrated that opsonic antibody binds to Tpr K and that the Tpr proteins are highly immunogenic in rabbits. Activated macrophages can phagocytize toxic treponemes, eliminating them from circulation. In a rabbit model, Tpr K varies in seven different places. Only homologous protection is offered by antibodies for these variable areas; they do not offer protection against heterologous strains(Leader Hevner et al. 2003). These TprK V region genes thirty vary as they are passed down over successive generations. Antigenic variation via gene conversion during illness has been believed as a further method using which the microbe evades the human immune response, allowing extended infection and survival in the midst of a robust host response. Similar processes have been identified in the syphilis-causing spirochetes belonging to the genus Borrelia (Morgan et al. 2003).

Because *T. Pallidum* cannot be grown for extended periods of time on artificial media, research into the pathophysiology of syphilis has been hampered. *T. Pallidum* can be passaged for a finite number of generations with a generation time of 30-33 h using monolayers of rabbit epithelial cells at 33-35 °C, but at this time, neither the quantity of organisms nor the flexibility in their manipulation make these techniques useful for studying *T. Pallidum*-host interactions. The most often used technique for producing organisms for study is in vivo propagation by inoculation of rabbit testis, which produces significant numbers of organisms (Edmondson et al. 2018).

2.6. STAGES OF SYPHILIS

2.6.1. PRIMARY STAGE

The early stages of syphilis often appear three weeks after bacterial encounter. A chancre, painless sore, appears at the infection site, most frequently on or close to the mouth, genitalia, and the abdomen. The chancre can persist for three to six weeks and frequently remains undetected, delaying diagnosis(Singh and Romanowski 1999; Brown and Frank 2003; Stamm 2016c).

2.6.2. SECONDARY STAGE

Syphilis normally progresses to the secondary stage four to ten weeks after the chancre first appears. The illness is now spreading throughout the body. One of the most typical symptoms is a non-itchy rash which appears on the soles of the feet, palms of hands, and the backs of the human body. Fever, exhaustion, a sore throat, pains in the muscles, enlarged lymph nodes, and hair loss are further symptoms. These symptoms may go away on their own in a few weeks or they may come and go even in the absence of medical care (Mattei et al. 2012).

2.6.3. LATENT STAGE

When syphilis is in its latent stage, there are no outward symptoms, but the infection can still be detected using a variety of serological tests, showing that the associated microbes are still present within the body. Years may pass during the latent period while the patient is not aware of their illness. Without treatment, the illness can advance to a later stage, or some people might never have any further symptoms (Essig and Longbottom 2015).

2.6.4. TERTIARY STAGE

Syphilis can advance to the tertiary stage if it is not treated, which can result in serious consequences that could be life-threatening. Typically, the appearance a tertiary stage follows a latent period that may last for few to many years. It damages several organs, causing degenerative lesions in the blood vessels, heart, brain, bones, joints, and other tissues. Tertiary syphilis symptoms might include dementia, inability to coordinate an individual's movements, paralysis, numbness, and blindness. The sexually transmitted spread of syphilis is extremely uncommon since there are so few treponemes present during tertiary syphilis. This stage can lead to neurological abnormalities, cardiovascular complications, blindness, deafness, and mental disorders (Stamm 2016a).

2.7. GUMMAS

The skin, bones, liver, or any other organ, such as the stomach and eyes, may develop little lumps or tumors known as gummas. The soft palate and the bones of the nose frequently develop gummas. The legs, trunk, face, and scalp are other frequent locations (Heston and Arnold 2018).

2.8. NEUROLOGICAL ABNORMALITIES

Syphilis can result in a variety of nervous system issues, including sudden, intense pains. People may vomit as a result of these painful spasms, which commonly damage the stomach among other organs. Additionally, you can get sudden, lightning-like sensations in your bladder, rectum, and throat. Syphilis may also make it more difficult for you to detect and respond to temperature changes. Stroke, meningitis (inflammation of the brain), visual problems, and blindness are all possible. Nervous system issues can also result in incontinence and impotence in men(Tramont 1987; Rufli 1989).

2.9. PITUITARY GLAND COMPLICATIONS

Rarely, syphilis can lead to hypopituitarism, a condition that occurs when the pituitary gland produces low amount of hormones than usual. In addition to other problems, this can result in accelerated aging in adults as well as dwarfism in children (Pekic and Popovic 2017).

2.10. CHILDBIRTH AND PREGNANCY COMPLICATIONS

If you develop syphilis while pregnant, your unborn child might get the disease. Infants who are infected are more likely to be born or to develop a variety of abnormalities. Infants who get syphilis from their mothers have a high risk of dying during or soon after delivery, and syphilis during pregnancy dramatically increases the chance of miscarriage or stillbirth (Benedetti et al. 2019; Manolescu et al. 2019).

2.11. GASTRIC COMPLICATIONS

This fairly typical condition, which most frequently affects people in their early 20s or 40s, has an impact on the stomach. It may result in discomfort, hunger loss, motion sickness, nausea, and weight loss (Choi et al. 2006).

2.12. CONGENITAL SYPHILIS

Congenital syphilis is a disorder that develops when a syphilis-infected pregnant mother transmits the virus to her fetus. Both the mother and the child's health and wellbeing are seriously at stake. If neglected, this treatable illness may result in fetal death, early delivery, or death soon after birth. Rash is one sign of congenital syphilis that neonates may experience other include fever, enlarged liver and spleen, anemia, and bone malformations (Cooper and Sánchez 2018; Rowe et al. 2018).

2.13. CLINICAL MANIFESTATIONS

There are a wide range of syphilis clinical manifestations and symptoms. Ocular, otic, or neurosyphilis syphilis can develop at any phase of the illness(Dourmishev and Dourmishev 2005; Forrestel et al. 2020). Syphilis' symptoms have been known for hundreds of years. In his description of the "French sickness" in 1514, Juan de Vigo mentioned genital pustule. The original chancre was accompanied by a reddish rash that was later recorded by several other people. This rash's apparent similarity to smallpox is what gave rise to the word "pox." Protean late manifestations affecting all organ systems are being observed, introducing syphilis as the "great imitator." A strong index of suspicion is still necessary for diagnosis (Singh and Romanowski 1999).

3. ANTIMICROBIAL RESISTANCE

The capacity of bacteria to resist and thrive while being targeted by antimicrobial drugs is known as antimicrobial resistance (AMR) (Abushaheen et al. 2020).
A major concern globally is the phenomenon of antimicrobial resistance (AMR). AMR, also known as acquired resistance, is the capacity of bacteria to withstand the effects of antimicrobial drugs that were earlier successful in treating illnesses brought on by such pathogens. Microorganisms like bacteria become insensitive to certain antibiotic treatments after developing resistance to them(Holmes et al. 2016; Frost et al. 2019).

3.1. MECHANISM OF AMR

As there are different ways by which antimicrobials can act on microbes similarly there are several ways in which microbes can evade antimicrobial drugs and develop resistance against them by making them no longer effective (Moo et al. 2020a).

3.1.1. LOW UPTAKE OF DRUG

Many factors play functional role in lowering and delaying the uptake of drug by bacterial cell Biofilms are one of them as they limit the penetration of drug within the cell by interfering with it and also by acting as a barrier between cell membrane and drug. Like P. aeruginosa, other microbes can produce a permeability barrier to prevent drugs from penetrating their cell membrane(Zhou et al. 2015).

3.1.2. DRUG INACTIVATION

Resistance can be acquired by neutralizing the effect of drug by using various mechanism like production of enzymes, β-lactamases are enzymes that hydrolyses the Beta-Lactam ring in case of Beta-lactams (Zhou et al. 2015; Pulingam et al. 2022).

3.1.3. DRUG EFFLUX

These efflux pumps play roles in transportation of molecules or antimicrobial drugs in and out of the cell and are of different types depending upon their functions. Multiple drug efflux pumps are the one aiding in resistance as they can transport a large number types structurally and functionally different drugs in and out of the cell (Uddin et al. 2021).

3.1.4. CHEMICAL MODIFICATIONS

It may be one of the prescription drugs, which is achieved by bacterial development of various enzymes that may connect to the drug and stop it from adhering to the target site, as is done using chloramphenicol when acetylation is carried out(Uddin et al. 2021), Or it can be of the target site like modifications in the penicillin binding proteins to decrease its affinity for beta-Lactams as observed in MRSA (Pulingam et al. 2022).

3.2. FACTORS CONTRIBUTING TO ANTIMICROBIAL RESISTANCE IN SYPHILIS

It appears that *T. Pallidum* is resistant to macrolides like azithromycin, which is brought on by point mutations or methylation of the peptidyl transferase region between nucleotide positions 2058 and 2059

in domain V of the 23S ribosomal RNA gene. *T. Pallidum* Street Strain-14 was the first strain to incorporate the A2058G mutation(Stamm 2015; Beale et al. 2019).
This resistance is caused by a change in the 23S rRNA target site carried by the mutation A2058/9G. There is currently widespread macrolide resistance to treat syphilis, including in Australia, Canada, China, Europe, and the USA (Tien et al. 2020b).
Tetracycline resistance in *T. Pallidum* isolates has been linked to mutations in the 16S rRNA gene(Wu et al. 2014). Additionally, recent examination of the *T. Pallidum* genomes revealed amino acid alterations in penicillin-binding proteins, however the therapeutic significance of these alterations is not yet clear. This finding serves as a reminder of the need to look for mutations in pertinent genes and assess the prevalence of resistances in a given area (Liu et al. 2021).
Additionally, it is believed that three penicillin-associated protein genes (tp0500, tp0760, and tp0705) and the 23S rRNA and 16S rRNA genes for possible mutations linked to antibiotic resistance in the *T. Pallidum* isolates (Liu et al. 2021).

3.3. GLOBAL TRENDS AND EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE IN SYPHILIS

Antimicrobial resistance (AMR) is a global issue that compromises the ability to effectively treat a variety of infectious illnesses, including syphilis (Dadgostar 2019). *Treponema pallidum* is the bacteria that causes the sexually transmitted disease syphilis. Syphilis is a chronic illness, and the only recognized natural host of *T. Pallidum* is the human. Direct sexual contact with acute primary or secondary sores is necessary for the transmission of syphilis. The emergence of antimicrobial resistance in syphilis is a growing problem that demands attention worldwide (LaFond and Lukehart 2006) .
Monitoring antibiotic resistance in syphilis is essential for informing public health policies and directing efficient treatment strategies. This involves monitoring the incidence of AMR strains, detecting risk factors linked to the emergence of resistance, and evaluating the effectiveness of novel therapeutic approaches. For countries to fully understand global patterns and adopt preventive actions, cooperation and data exchange are critical(Klaucke et al. 1988; Crofts et al. 1994).
A combined approach is required to address the worldwide threat of AMR. This involves enhancing surveillance programmes, encouraging appropriate antibiotic use(Dadgostar, 2019) funding the discovery of novel antimicrobial medicines, and increasing public and professional knowledge. Syphilis must be treated as a top priority in terms of global health issues, and everyone needs access to appropriate treatment alternatives (Majumder et al. 2020b).

4. MECHANISMS OF ANTIMICROBIAL RESISTANCE IN SYPHILLIS

4.1. GENETIC MECHANISM

4.1.1. GENETIC MECHANISM OF AMR IN SYPHILIS

Antimicrobial resistance (AMR) is the term used to describe a microorganism's capacity to endure and proliferate in spite of being exposed to antibiotics. A sexually transmitted infection called syphilis is brought on by the bacterium *Treponema pallidum*. The genetic mechanisms underlying AMR in syphilis are poorly known, despite indications of rising resistance to several antibiotics used to treat syphilis, such as azithromycin (Liu et al. 2021).
Nevertheless, there are a few potential mechanisms that could contribute to amr in syphilis:

4.1.2. TARGET GENE MUTATIONS

Bacteria can acquire resistance by mutations in the genes targeted by antimicrobial medications. For instance, if a particular antibiotic works by attaching to a specific protein involved in bacterial replication or metabolism, mutations in the gene producing that protein may block or diminish the drug's ability to bind to that protein, rendering the medicine useless (Giedraitienė et al. 2011).

4.1.3. EFFLUX PUMPS

Efflux pumps are proteins that actively pump medicines out of the bacterial cell. They can be found in bacteria. By doing this, they can lessen the drug's effectiveness by lowering its concentration inside the cell. AMR may be facilitated if syphilis bacteria produce efflux pumps that can expel antibiotics (Giedraitienė et al. 2011).

4.1.4. ACQUISITION OF RESISTANCE GENES

Through horizontal gene transfer, bacteria can obtain resistance genes from other bacteria. Processes like conjugation, transformation, or transduction may be used to achieve this. It is possible to develop resistance to syphilis if the bacteria that cause it pick up resistance genes from other bacteria that are already resistant to particular antibiotics (Roe and Pillai 2003).
It's important to keep in mind that the precise genetic processes causing AMR in syphilis haven't been well investigated or defined yet. In order to create efficient preventative and treatment plans for syphilis, further study is required to better understand the genetic basis of antibiotic resistance in this disease.

4.2. MOLECULAR MECHANISM OF RESISTANCE OF AMR IN SYPHILIS

A sexually transmitted infection called syphilis is spread on by the bacterium *Treponema pallidum*. Similar to other infectious diseases, antibiotic resistance in syphilis develops when the bacteria mutate and build defenses against antibiotics. Penicillin or its derivatives, the recommended treatment for syphilis, were quite effective as shown in Fig. 2 (Stamm , 2010).
However, it is crucial to remember that antibiotic resistance may develop in any bacterial illness, including syphilis. If resistance developed, it would probably be the result of genetic mutations or the acquisition of resistance genes through horizontal gene transfer. Other microorganisms that have gained antibiotic resistance frequently exhibit these methods (Baker et al. 2018).
Depending on the particular antibiotic and bacterium involved, different molecular pathways might cause bacteria to become resistant to antibiotics (Roe and Pillai, 2003). A broad review of some typical ways by which bacteria acquire antibiotic resistance are as follows:

4.2.1. EFFLUX PUMPS

The concentration and efficiency of antibiotics can be decreased by bacteria producing efflux pumps that aggressively pump them out of the bacterial cell (Abebe et al. 2016).

4.2.2. TARGET SITE MODIFICATIONS

Bacteria can change the enzymes or proteins that antibiotics target to make them less vulnerable to the medications (Blair et al. 2015).

4.2.3. ENZYMATIC INACTIVATION

Antibiotics can lose their efficacy due to the production of enzymes by bacteria.
Reduced permeability: The effectiveness of antibiotics can be decreased by bacteria altering their cell membranes to prevent drug entrance (Abebe et al. 2016).

4.2.4. ANTIBIOTIC MODIFICATION

Antibiotics can lose their effectiveness when bacteria develop enzymes that change them chemically (Fig. 1) (Gupta and Birdand 2017).
It is crucial to underline that penicillin or its derivatives continue to be the suggested treatment for syphilis and that antibiotic resistance is not currently a serious concern. To stop the emergence and spread of antibiotic-resistant strains of any bacterial infection, however, it is essential to maintain surveillance and use antibiotics responsibly. For the most recent information and suitable treatment choices, it is essential to speak with a healthcare provider if you suspect you have syphilis or are worried about antibiotic resistance (Liu et al. 2021).

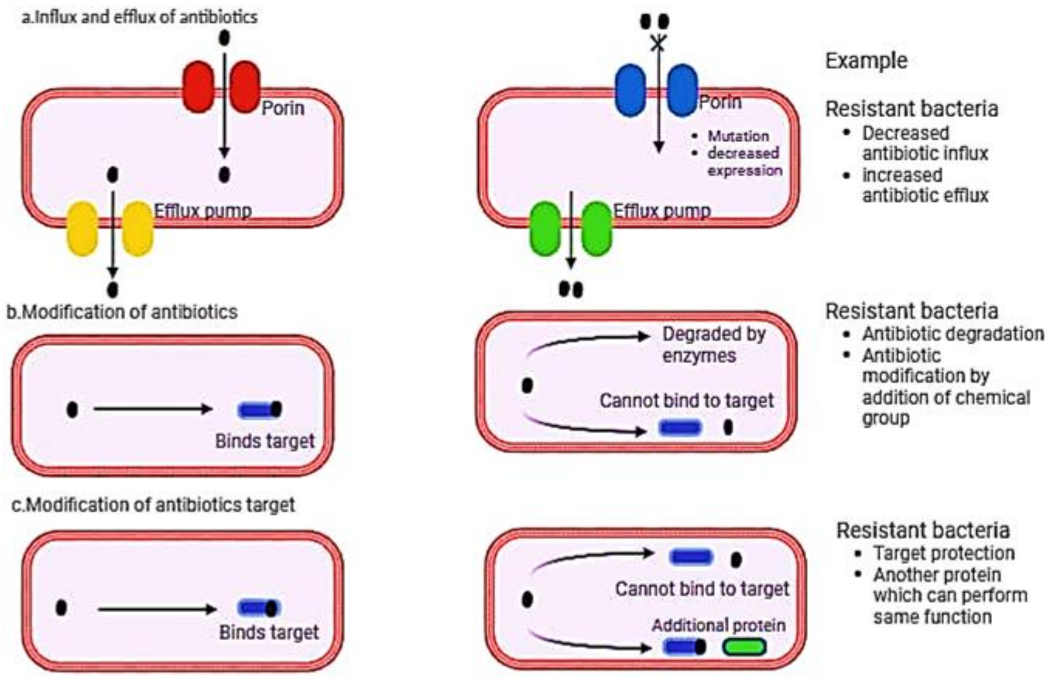

Fig. 1: Mechanism of AMR in bacteria.

4.3. ACQUISITION OF ANTIMICROBIAL RESISTANCE (AMR)

4.3.1. SPONTANEOUS MUTATION

Resistance can be acquired by bacteria, including *Treponema pallidum*, by unintentional alterations in their DNA. These mutations may naturally take place during DNA replication and may result in alterations to specific bacterial genes that are susceptible to antibiotic action. As a result, the bacteria develop an immunity to the antibiotics' actions (Che et al. 2021).

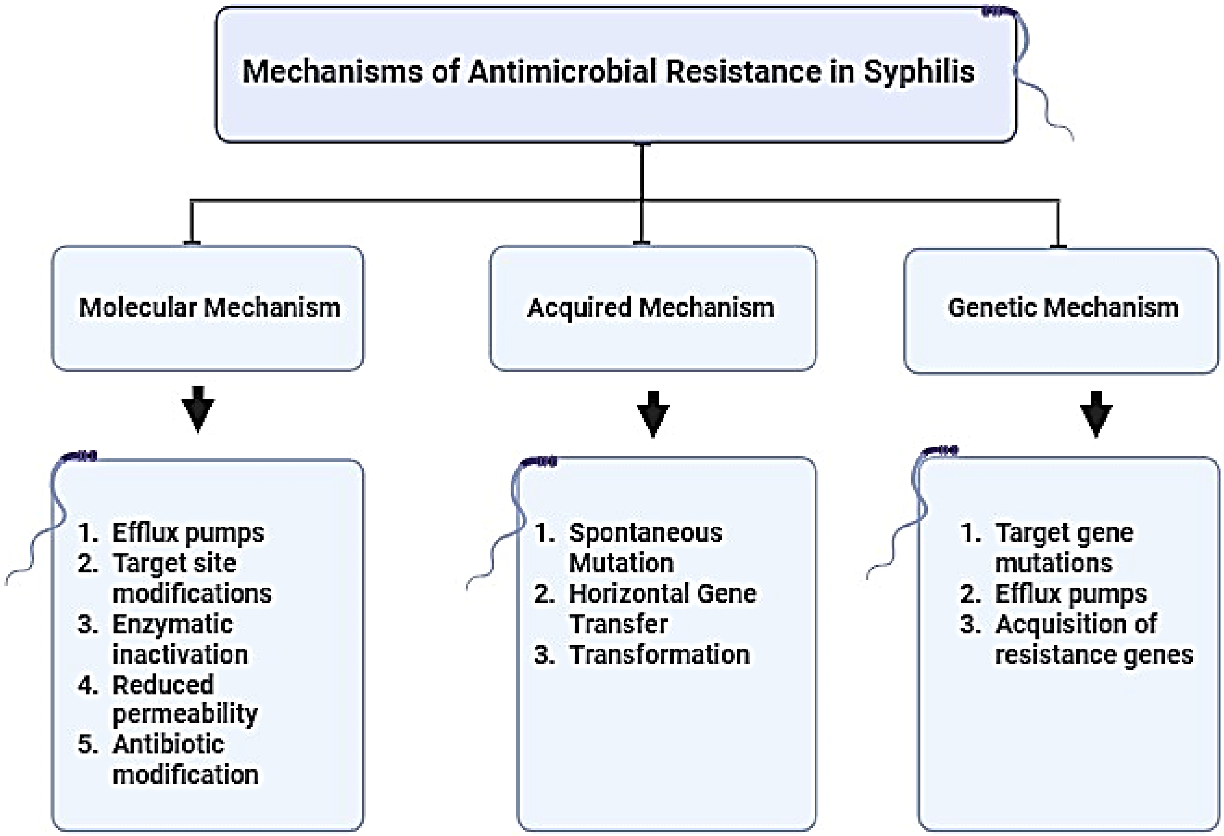

Fig. 2: Mechanism of AMR Syphilis.

4.3.2. HORIZONTAL GENE TRANSFER

This is a crucial way by which bacteria acquire AMR genes. Genetic material is exchanged between various bacteria, even those of different species. The following are the top three horizontal gene transfer mechanisms: a. Conjugation: During conjugation, two bacteria physically unite by means of a pilus, which resembles a bridge. Plasmids (tiny, circular DNA molecules) encoding AMR genes are transferred from the donor bacteria to the receiving bacterium as shown in Fig. 3. (Baker et al. 2018).

4.3.3. TRANSFORMATION

Bacteria transform by consuming free DNA pieces from their surroundings, which may contain AMR genes. The resistance is conferred via the integrated DNA, which is incorporated into the recipient bacterium's genome (Che et al. 2021).

4.3.4. TRANSDUCTION

Through the use of a bacteriophage, a bacterial virus, genetic material is transferred between bacteria during transduction. It is possible for the bacteriophage to unintentionally package and transfer bacterial DNA, including AMR genes, to another bacterium throughout the course of an infection (Jamil et al. 2023).

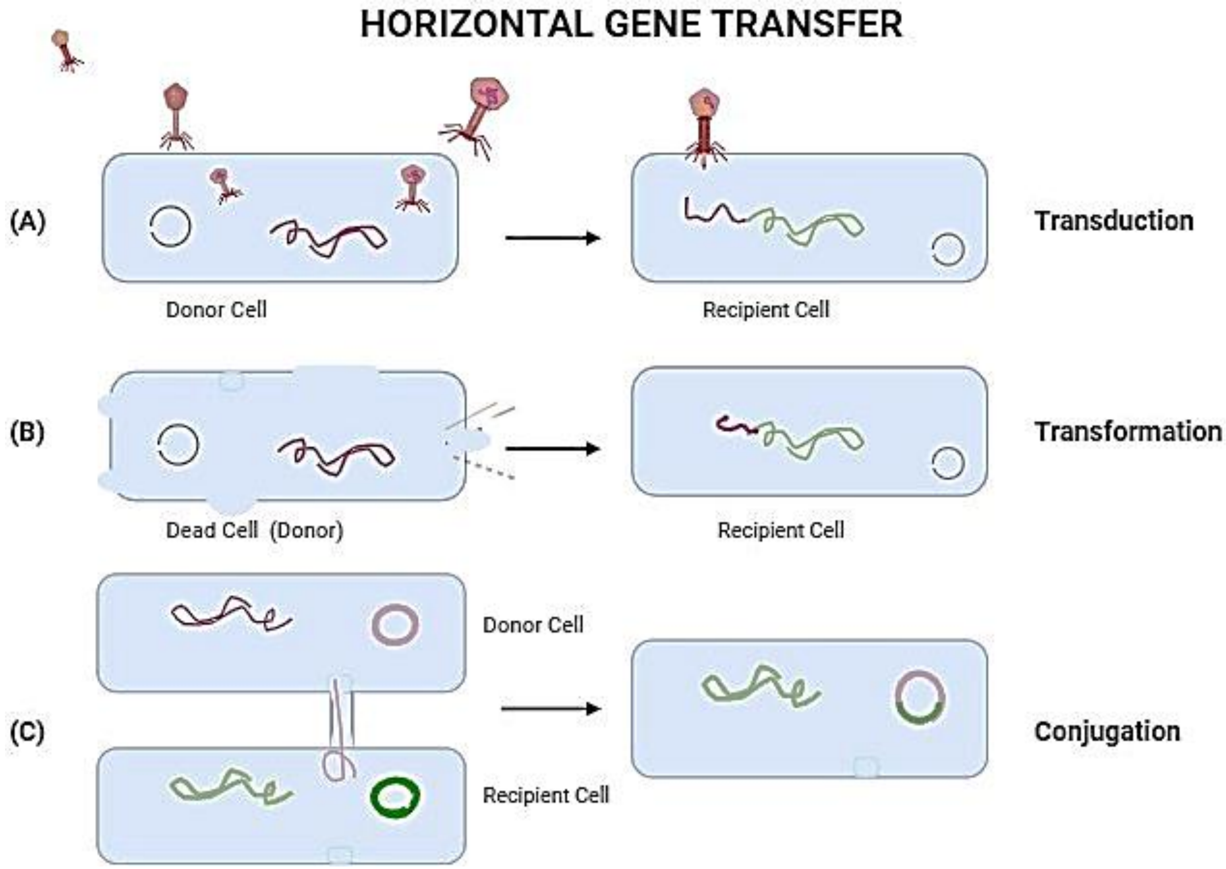

Fig. 3: Horizontal gene transfer.

4.4. EVOLUTIONARY ASPECTS OF ANTIMICROBIAL RESISTANCE IN SYPHILIS

Antimicrobial resistance (AMR) in syphilis has become a troubling problem over time. The bacteria *Treponema pallidum* is the source of the sexually transmitted disease syphilis. Penicillin has been the mainstay of syphilis treatment for many years and is still quite successful today. Antibiotic-resistant *T. Pallidum* strains have, nevertheless, started to appear in recent years (Roe and Pillai 2003). Here are some key evolutionary aspects of antimicrobial resistance in syphilis:

4.4.1. NATURAL SELECTION

Natural selection is what causes the syphilis antimicrobial resistance to emerge. Antibiotics used to treat syphilis put the bacteria under selective pressure, favoring the survival and reproduction of those with genetic mutations or other resistance-granting processes. These resistant strains increase in population prevalence over time (Santos-Lopez et al. 2021).

4.4.2. GENETIC MUTATIONS

An important factor in the emergence of antibiotic resistance is genetic mutation. In the case of syphilis, mutations can develop in genes involved in antibiotic uptake, efflux, or modification, as well as in genes responsible for the binding of penicillin to the target location within the bacteria. These alterations may change the bacterial target's structure or function, making it less vulnerable to the antibiotic's effects (Barbosa and Levy 2000).

4.4.3. HORIZONTAL GENE TRANSFER

Antimicrobial resistance in syphilis can be acquired through horizontal gene transfer in addition to genetic alterations. The transfer of resistance genes between diverse bacteria, including unrelated species, is a part of this process. Plasmid exchange, transposon-mediated transfer, and bacteriophage-mediated transfer are a few examples of methods that might result in horizontal gene transfer. The receiving bacteria can quickly develop resistance features thanks to this transfer of resistance genes (Baker et al. 2018).

4.4.4. ANTIBIOTIC MISUSE AND OVERUSE

Antibiotic misuse and overuse are major factors in the emergence and dissemination of antimicrobial resistance in syphilis. Self-medication, incorrect antibiotic use, and inadequate or incomplete treatment plans can all contribute to the selection and spread of resistant bacteria. Antibiotic usage is common in many industries, including medicine, agriculture, and animal husbandry, which accelerates the creation and spread of resistance (Moo et al. 2020b).

4.4.5. GLOBAL DISSEMINATION

Antimicrobial resistance to syphilis is not isolated to any particular area. The international movement of people, including migration and travel, promotes the cross-border transmission of resistant strains. These resistant strains can further evolve and adapt to local conditions once they are established in a new population, which adds to the continuous difficulty in properly treating syphilis (Stamm 2010).

4.5. RATIONAL USE OF ANTIBIOTICS

Rational use of drugs requires that patients must be given medication appropriately to their clinical needs, at the lowest cost to them and their community, for an adequate period and in doses that meet their particular needs (WHO 1988). In short,

4.5.1. PROPER INDICATION

(antibiotics only prescribed for serious infections)

4.5.2. PROPER DRUG

(for disease, bacterium, patient conditions)

4.5.3. PROPER DOSAGE

(patient characteristics- weight, renal function, interactions)

4.5.4. COST EFFECTIVE

(should not be expensive)

4.5.5. PROPER TIME

(not too late, not too early)

4.5.6. PROPER DURATION

(for the disease to be cured)
Presently, there is no vaccine available to prevent syphilis. Antibiotics are among the most consistently used drugs of choice for treatment of syphilis globally. Doxycycline and macrolide were used as alternative therapies. At the present time massive use of Macrolides causes its resistance in syphilis patients in many geographical regions including Australia, Canda, China and Europe. Antimicrobial resistance poses severe threats to human healthcare costs and dramatically increasing resistance causes mortality as well as morbidity (Tien et al. 2020a).
Irrational use of antibiotics are main drivers in the development of drug resistance among syphilis patients. Antimicrobial resistance causes the antibiotics to become less effective, as well as cause adverse health effects and it becomes hard to treat patient with serious infectious diseases.
In order to address the growing issue of antimicrobial resistance in syphilis, it is essential to encourage appropriate antibiotic use, create novel treatment options, improve monitoring systems to track patterns of resistance, and fund studies to comprehend the genetic mechanisms underlying resistance. In addition, public health initiatives including thorough sexual education, improved access to screening and care, and the application of combination therapy can lessen the effects of antibiotic resistance in syphilis (Barbosa and Levy 2000).

5. DIAGNOSTIC CHALLENGES IN ANTIMICROBIAL RESISTANCE

Syphilis can be treated and cured with antibiotics, but if left untreated, it can cause serious health problems, such as damage to the heart, brain, and other organs. It is important to practice safe sex and get tested for syphilis regularly to prevent the spread of the disease. The text is talking about a part of the brain called the pallidum. In the late 1990s, many people believed syphilis was no longer a concern. Many years later, this hidden disease became a problem for public health again. It affected certain groups of people more, like men who have sex with men, people living with HIV, female sex workers, male sex workers, people in prison, and pregnant women (Workowski and Bolan 2015a),
In 2017, the CDC said that 15-20% of individuals in the United States have a certain problem or condition. In the past, they had a syphilis infection, and from 2013 to 2017, there was a 76% rise in infection cases. According to the Health Data Organization, about 49. 7% of syphilis cases worldwide have been estimated to be prevalent. For women, about 18. 7% of them have this condition. And for men, about 31% of them have it. It seems that there are a lot of men getting sick again worldwide. The World Health Organization (WHO) says that around 7 million people got syphilis for the first time in 2020.
Even though syphilis is required to be reported in every country, it becomes a bigger issue when it doesn't show any symptoms. Many people with acquired syphilis, around 43%, do not show any signs of the disease. Because of these things, the illness could be wrongly identified by doctors. Many countries, like Mexico, do not have a lot of information or reports. We really need proof that there are more cases happening, and we have to be extra careful because this old enemy is affecting people who are already in a tough situation (Dombrowski et al. 2015; Mabey et al. 2006).

5.1. CURRENT DIAGNOSTIC METHODS FOR SYPHILIS

5.1.1. SEROLOGICAL TESTS

Serological tests are the main way to diagnose syphilis. They work by finding specific antibodies that the immune system makes to fight T, which causes syphilis. Pallidum is a difficult word to simplify, but it refers to a part of the brain. These tests can be put into two main groups: tests that are not for syphilis (Non-treponemal Tests) and tests that are for syphilis (Treponemal tests) (Dombrowski et al. 2015).

5.1.2. NON-TREPONEMAL TESTS

They find antibodies that attack cardiolipin, which is a part of cells that are harmed. The two most common tests used for certain diseases are the VDRL test and the RPR test. These tests can sometimes be sensitive but might give incorrect positive results, especially in patients who have other infections or autoimmune disorders (Workowski et al. 2021).

5.1.3. TREPONEMAL TESTS

Treponemal tests can find antibodies that specifically target the bacteria called Treponema. Pallidum antigens are substances found in the body that can be used to detect a specific disease. They are very precise, but not often used for first testing because they sometimes give incorrect positive results. Enzyme immunoassays (EIA) and fluorescent treponemal antibody absorption (FTA-ABS) are two common tests used in medical practice (Workowski et al. 2021; Ong et al. 2018).

5.2. MOLECULAR DIAGNOSTIC TESTS

Molecular diagnostic tests like PCR and NAATs can find T directly. Pallidum DNA or RNA means the genetic material of the pallidum organism. These tests are very good at finding if someone has syphilis, especially during the early stages when the body may not have produced enough antibodies to detect the disease. However, they cost a lot of money and may not be easily found in all healthcare places, (Orbe-Orihuela et al. 2022a).

5.3. POINT-OF-CARE TESTS (POCTS)

Point-of-care tests (POCTs) are fast diagnostic tests that can be done at the bedside or in the field, giving quick results. Some tests for syphilis can detect specific antibodies. Although convenient, these tests may not be as good at detecting things as tests done in a laboratory (Organization 2016).

5.4. DARK-FIELD MICROSCOPY

Dark-field microscopy is a way to look at samples under a special microscope that makes them easier to see. It's often used to examine things like genital sores or wounds. This technique helps us see T more easily. Pallidum motility means the movement of a certain type of bacteria called pallidum. It can help doctors make a quick guess about a person's illness. However, not everyone may have the necessary skills, and it may not be easily found (Ong et al. 2018).

5.5. SEROLOGICAL ALGORITHM

To make sure syphilis is diagnosed correctly, doctors often use a serological algorithm. This algorithm takes into account the strengths and limitations of different tests to improve the accuracy of the diagnosis. This method uses various tests in a certain order. It starts with one kind of test and if it shows positive results, another kind of test is used to confirm it (Janier et al. 2014).

5.6. POTENTIAL ISSUES IN DETECTING RESISTANCE OF SYPHILIS

Recognizing resistance to anti-microbials in syphilis is basic for viable treatment and administration of the malady. In any case, a few potential issues and challenges may emerge within the handle of distinguishing resistance in syphilis cases. This chapter points to supply a point by point diagram of these potential issues, which can complicate resistance location endeavors and affect persistent care (Wu et al. 2012).

5.6.1. LOW AWARENESS AND TESTING

One of the main problems in finding resistance in syphilis is that healthcare providers are not aware that resistance is possible. Because penicillin has been effective in treating syphilis in the past, doctors may not always think about resistance as the reason why treatment is not working. This means that sometimes, resistance testing that can help detect things early is not done, causing missed chances to find problems sooner (Organization, 2016). (Siedner et al. 2004).

5.6.2. OVERRELIANCE ON NON-TREPONEMAL TESTS

In regular medical practice, tests like the RPR and VDRL are commonly used to screen for syphilis. While these tests are sensitive, they require accuracy, which can lead to false-positive results. If serological tests don't show the desired results or if treatment doesn't work, healthcare providers might not think about resistance right away because the information from non-treponemal tests is limited (Organization 2016).

5.7. CHALLENGES IN REFINED TREPONEMA PALLIDUM

The bacteria called *Treponema pallidum* is the main cause of syphilis. This type of bacteria can actually be difficult and take a long time to treat. The bacteria have strict needs and are particular, making it hard to find usable samples for testing their vulnerability. So, it may not always be possible to do resistance testing based on culture, especially in places with limited resources (Workowski et al. 2021).

5.8. LACK OF STANDARDIZED METHODS FOR RESISTANCE TESTING

When there are no standard rules for testing resistance in syphilis, different labs and areas may use different methods for testing. This lack of sameness can make it hard to compare resistance data and make it difficult to fully understand resistance patterns (Workowski et al. 2021).

5.9. GENETIC HETEROGENEITY OF TREPONEMA PALLIDUM

Treponema pallidum is a type of germ that can have different genes, and some types might be more or less sensitive to antibiotics. The bacterium having different genetic characteristics can make it difficult to accurately predict and detect resistance because different strains may have different ways of resisting (Janier et al. 2014).

5.10. SMALL SAMPLE SIZES

Syphilis resistance is not very common compared to other types of infections. So, when researchers study resistance, they sometimes only have a small number of people to study. This means they might not have enough data to accurately understand how common resistance is (Janier et al. 2014).

6. DIFFICULTY IN DISTINGUISHING REINFECTIONS FROM TREATMENT FAILURES

Differentiating between when a treatment isn't working and when someone gets infected again with a different type of T. "Pallidum can be difficult." People getting infected again can have the same symptoms as before. This might be mistaken as the treatment not working, leading to a wrong diagnosis (Wu et al. 2012).

7. LIMITED AVAILABILITY OF MOLECULAR TECHNIQUES

The use of advanced methods, like whole-genome sequencing, can give us important information about mutations that cause resistance. However, not all healthcare places have these methods available, especially in areas with limited resources (Dombrowski et al. 2015; Cantor et al. 2016).

8. ETHICAL CONSIDERATIONS

Resistance testing in syphilis involves taking samples from patients to see if the infection is resistant to treatment. However, it may not always be possible or acceptable to collect these samples from patients. The ethical concerns of collecting samples from private areas like genital sores may affect how resistance testing is done (Dombrowski et al. 2015; Cantor et al. 2016).

8.1. EMERGING DIAGNOSTIC TECHNOLOGIES FOR ANTIMICROBIAL RESISTANCE IN SYPHILIS

People are worried about syphilis becoming resistant to antibiotics. This has led to research to find better ways to diagnose it. It is very important to find resistance quickly and correctly, so we can give the right treatment and avoid treatment not working. This chapter talks about new tools that can help us diagnose if a person is resistant to antibiotics for syphilis. These tools can help us understand how resistance works and help us choose the right treatment for each person.

8.2. MOLECULAR-BASED RESISTANCE DETECTION

8.2.1. WHOLE-GENOME SEQUENCING (WGS)

Is a technique that helps scientists find out the full genetic code of the *Treponema pallidum* strain causing an infection. WGS can find genetic changes linked to resistance to medicines. This method gives detailed information about the pathogen's genetic make-up, which helps understand how it becomes resistant to treatments. WGS can help keep track of resistance trends and better understand the genetic differences of *T. Pallidum* strains are types of bacteria that are weak or pale in color (Cantor et al. 2016).

8.2.2. POLYMERASE CHAIN REACTION (PCR)-BASED ASSAYS

PCR tests are commonly used in labs for diagnosing things because they are really good at detecting specific things and are very accurate. We can make special tests called PCR assays that target specific genes in syphilis which are linked to resistance against antimicrobial drugs. For instance, changes in the 23S rRNA gene have been connected to macrolide resistance in *T. Pallidum* is a word that means a pale or light color. PCR tests can quickly find mutations that cause resistance to medicine. Doctors can use different samples like swabs from private parts or blood to do these tests (Grimes et al. 2012).

8.3. NEXT-GENERATION SEQUENCING (NGS)

New sequencing technologies have greatly changed genomic research and are now being used more often to study diseases like syphilis. NGS is a technology that can quickly read the DNA code of many samples at once. Next-generation sequencing (NGS) can give us in-depth information about the variety of genes in T. We study groups of pallidum bacteria and find mutations that make them resistant to treatment in patient samples (Tien et al. 2020a). (Cantor et al. 2016)

8.4. DIGITAL POLYMERASE CHAIN REACTION (DPCR)

This technology can be used to find uncommon strong types of T. The pallidum is not affected by most strains. Digital PCR (dPCR) is a better and more accurate type of PCR than the traditional one. It can be really useful in keeping track of how resistance is developing and spreading (Tien et al. 2020a).

8.5. MASS SPECTROMETRY-BASED TECHNIQUES

Scientists have used a method called mass spectrometry, specifically one called matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, to identify bacteria that cause diseases. This method has been effective. We can use these methods to find proteins or biomarkers that show resistance in *T. Pallidum* can be described in simpler terms as a part of the brain. Mass spectrometry techniques can quickly and accurately study bacterial proteins, and may be useful for identifying resistance (Orbe-Orihuela et al. 2022a).

8.6. MICROFLUIDIC-BASED ASSAYS

Microfluidic technologies are small platforms used for different diagnostic tests. These tests have benefits like needing less sample and chemicals, analyzing quickly, and possibly being used at the patient's location. Microfluidic-based tests can be created to find specific resistance markers or check how effective antibiotics are against infections using patient samples (Orbe-Orihuela et al. 2022a).

8.7. MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE (AI)

Machine learning and AI can be used to study big sets of data collected from genetic sequencing or other diagnostic methods. These methods can help find connections between genes and resistance to syphilis, which can help predict and detect resistance earlier (Tucker et al. 2010).

8.8. METAGENOMIC SEQUENCING

Metagenomic sequencing is a technique used to study different types of germs found in a sample from a sick person. This method can find T. Study the genetic makeup of pallidum and identify resistance markers without growing bacteria. Metagenomic sequencing is a new method that shows potential for quickly and thoroughly detecting resistance (Grimes et al. 2012).

8.9. IMPACT OF ANTIMICROBIAL RESISTANCE

8.9.1. CLINICAL IMPLICATIONS OF RESISTANT SYPHILIS INFECTION

Syphilis is transmitted by sexual contact and is caused by the bacterium *Treponema pallidum*. It can have substantial clinical implications if left untreated.

8.10. PUBLIC HEALTH CONSEQUENCES

Resistant syphilis infection, also called as antibiotic-resistant syphilis, is a serious public health concern due to the following consequences

8.10.1. INCREASED TRANSMISSION

Syphilis strains that are resistant to treatment may spread more readily among people in a community. Syphilis outbreaks could result from this, especially in high-risk groups like those who engage in sex work and males who have intercourse with other men (Fernandes et al. 2015).

8.10.2. DELAYED TREATMENT AND DIAGNOSIS

Usually it is more difficult to detect the strains of resistant syphilis by using standard methods of testing as it lead to late diagnosis. Delayed identification and treatment can lengthen the course of the infection, raise the risk of consequences, and keep the transmission of disease to other people (Bowen et al. 2015).

8.10.3. LIMITED TREATMENT CHOICES

Resistant syphilis strains decrease the efficacy of conventional antibiotics for syphilis, like penicillin. This restricts treatment choices to make it more challenging to efficiently control and manage syphilis infection (Workowski and Bolan 2015)

8.11. HEALTH CARE IMPLICATIONS

8.11.1. RISK ASSESSMENT

Syphilis education must be a important part of STI interventions, along with the ability to obtain accurate sexual histories from patients. Concentrating on "sexual health" as opposed to "sexual illness" is vital due to the latter's negative meaning, which might make patients feel more relaxed discussing sex with their doctor (Nelson 2014).

Additionally, it is crucial to note that if the lesion is not shielded by the condom, condoms are less effective in preventing infections like syphilis (as well as chancroid and maybe herpes simplex virus and human papillomavirus) that are spread through sores.

In the clinical context, handouts with Internet and social media links to support in-office talks might be useful (Workowski and Bolan 2015a)

8.12. SCREENING

Numerous studies propose insufficient provider adherence to STI screening procedures; they include poor syphilis testing rates among HIV-positive people, missed chances to prevent congenital syphilis cases and also low syphilis testing for women who gave birth to stillborn children. Third party spenders should think about introducing reimbursement inducements that reward health systems for improved screening practices, and health care systems should work to implement quality control activities that track provider adherence to syphilis screening (Patel et al. 2017).

8.13. PUBLIC HEALTH'S ROLE

Successful illness therapies require the involvement of public health (containing municipal, state, and federal health departments) at all levels, from the individual to the public policy levels. Public health can persuade lawmakers to make rules that decrease obstacles for those who require medical preventative treatments and guarantee the financial stability of STI clinics.

Public health can also make sure that healthcare professionals are properly educated and trained about syphilis in terms of prevention, interpreting diagnostic tests, suggestions for therapy, and current disease incidence surveillance (Schmidt et al. 2019).

8.14. ADDITIONAL TREATMENT OPTIONS

Additional therapy choices are another area of biomedical research that is in requirement. *T. Pallidum* has not yet shown any signs of penicillin resistance, although syphilis therapy has not advanced in 75 years.

According to the CDC, penicillin is the solitary available therapy for pregnant women to prevent congenital syphilis and it gets worse by the presence of penicillin allergies

Ceftriaxone is a alternative for penicillin that the World Health Organization (WHO) classifies as having "very low quality evidence" in situations when it is either not available or desensitization is not a choice for pregnant women (Workowski and Bolan 2015a).

9. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

9.1. PROMISING AREAS OF RESEARCH ON ANTIMICROBIAL RESISTANCE IN SYPHILIS

One of the most important areas of study involves creating novel syphilis therapies. Penicillin, which has been used to treat syphilis for more than 70 years, is currently the first line of defence. However, the increase of *T. Pallidum* resistance strains has occasionally rendered penicillin useless. Alternative antibiotics like macrolides, cephalosporins, and tetracyclines are being researched. Azithromycin, which is frequently used to treat other STDs including chlamydia and gonorrhea, may be useful in treating early syphilis, according to recent research. Further research is required to evaluate azithromycin's long-term effectiveness because it has also been observed that some bacteria are resistant to it. (Clement et al. 2014; Stamm 2015).

In order to identify *T. Pallidum* DNA in blood or urine samples, researchers are investigating novel diagnostic methods including loop-mediated isothermal amplification (LAMP) and polymerase chain reaction (PCR). Studies are being conducted to determine these tests' accuracy and viability in clinical settings since they have demonstrated encouraging results in detecting early-stage syphilis. (Larsen et al. 1995; Luo et al. 2020).

Another crucial area of study is figuring out how *T. Pallidum*'s molecular mechanisms of resistance work. Penicillin-binding proteins (PBPs), which are the target of penicillin, are assumed to be the source of antibiotic resistance in *T. Pallidum* due to gene mutations. According to research, *T. Pallidum* contains three PBP homologs, and changes in any of these genes can result in penicillin resistance. Targeting these genes is a topic of research (Liu et al. 2021).

9.1.1. INNOVATIVE APPROACHES TO COMBAT RESISTANCE IN SYPHILIS

A serious concern to world health is antimicrobial resistance. However, the existing pipeline of antibiotics lacks enough innovation to address this challenge due to a commercial framework that does not give a return on investment, which discourages investment in antibiotic R&D. The antimicrobial stewardship program, which is in charge of defining, promoting, and monitoring the appropriate use of antibiotics, is crucial in tackling current issues (Vickers et al. 2019). In Addition to Antimicrobial Stewardship Program other innovative approaches to combat resistance in syphilis include Antibiotic combination therapy, developing Nanotechnology-based Therapies (Worthington and Melander 2013; Murugaiyan et al. 2022; Koh et al. 2023). Here we discussed these approaches one by one:

9.1.2. Antimicrobial Stewardship Program

Antimicrobial stewardship strategies are coordinated initiatives within a healthcare environment that support the prudent application of antibiotics, enhancing patient outcomes, lowering antibiotic resistance, and limiting the spread of diseases brought on by antibiotic-resistant microorganisms (Srinivasan 2017; Vickers et al. 2019). In this section, we'll look at a few of these innovative strategies and see how effectively they could work against resistance:

9.1.3. Optimizing Treatment Regimens

Antimicrobial stewardship programs are essential for optimizing treatment regimens in combating against syphilis resistance. They make sure that patients get the best antibiotics at the right dosages and intervals (Doron and Davidson 2011). Antimicrobial stewardship programs lessen the possibility of treatment failure and the consequent establishment of resistance strains by using a patient-centered approach (MacDougall and Polk 2005).

9.1.4. PROMOTING SAFE USE OF ANTIBIOTICS

Antimicrobial stewardship programs provide a strong emphasis on the safe use of antibiotics, specifically for treating syphilis. This involves educating medical professionals about the proper uses, doses, and time periods for antibiotic treatment (Doron and Davidson, 2011). For example, Penicillin is the only CDC-recommended regimen for the treatment of syphilis during pregnancy and the prevention of congenital syphilis in the newborn (Workowski and Bolan 2015b)

9.1.5. COLLABORATION AND EDUCATION

The training and education of medical professionals and students on prudent antimicrobial prescription or antimicrobial stewardship is necessary for reducing antimicrobial resistance since it is linked to antibiotic abuse. Healthcare professionals collaborate to put stewardship initiatives into action and enforce them, including physicians, chemists, and microbiologists. Initiatives to educate healthcare professionals on the value of safe antibiotic usage and the effects of resistance on syphilis. These programs also inform patients of the need of adhering to their recommended treatment plans, emphasizing the overall effectiveness (Majumder et al. 2020a)

9.1.6. ANTIBIOTIC COMBINATION THERAPY

A combination of treatments is one of the most effective methods for overcoming syphilis resistance. While a single antibiotic is often used throughout the course of therapy for syphilis, combining different antimicrobial drugs can increase the efficacy of the treatment and lower the risk of resistance emerging. Antibiotic combinations such benzathine penicillin, doxycycline, and azithromycin have been studied for their synergistic effects. Combination treatment enhances patient outcomes, has greater rates of effectiveness, and stops the emergence of resistance (Worthington and Melander 2013; Stamm 2015; Murugaiyan et al. 2022; Koh et al. 2023).

9.2. NANOTECHNOLOGY BASED THERAPIES

Antibiotic resistance may now be treated in novel ways thanks to the application of nanotechnology in medicine. Nanoparticles can deliver antibiotics more efficiently and increase medication penetration by getting to places that are challenging for traditional medicines to reach. In addition, researchers are looking at the possibility of using nanoparticles as carriers for gene-editing instruments like CRISPR/Cas9 to target particular antibiotic-resistant genes in *Treponema pallidum* making the bacteria susceptible to therapy. These developments in nanotechnology have the potential to completely transform the way syphilis is treated and successfully deal with resistance (Wan et al. 2021).

9.3. POTENTIAL STRATEGIES FOR PREVENTING RESISTANCE EMERGENCE

Even if there are no symptoms, syphilis can be transmitted through sexual contact with an infected individual. Consequently, a combination of personal and public health actions is needed for syphilis prevention (Klaucke et al. 1988).
Potential strategies for preventing the emergence of syphilis has been mentioned in Fig. 4 which includes:

9.3.1. SURVEILLANCE SYSTEM

Monitoring the changing patterns and trends of syphilis occurrences and outbreaks, sorting out at-risk groups, and measuring the effectiveness of treatments all lie under this category (Catchpole, 1996). The establishment and execution of successful preventative programmes can be promoted by surveillance data. In order to ensure that only significant problems are being monitored while ensuring that surveillance systems are operating effectively, analysis of surveillance systems must encourage the best possible use of public health resources (Klaucke et al. 1988).

9.3.2. SEX EDUCATION

Since there is no vaccine to prevent syphilis, it is crucial to promptly diagnose and treat infected people and their sexual partners as part of syphilis prevention programmes that involve the use of condoms

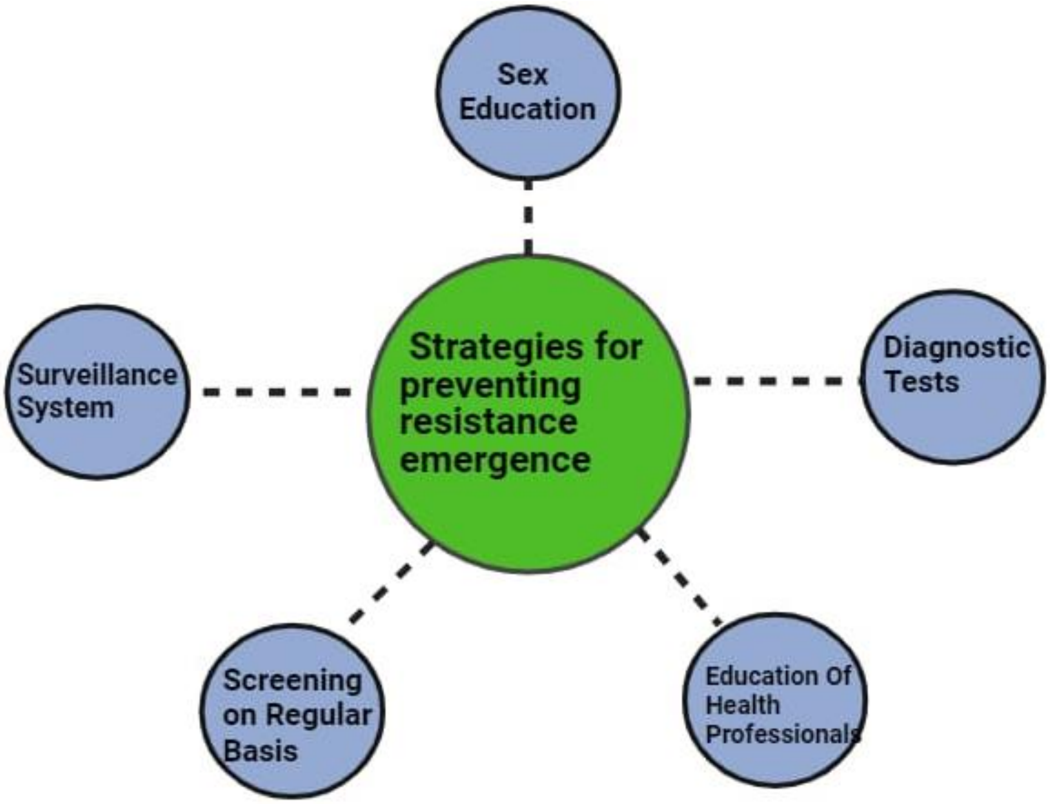

Fig. 4: Potential Strategies for Preventing Resistance Emergence.

promotion & sex education (Stamm 2016b). In order to minimize sexual activity's exposure to contaminated body fluids, physical barriers must be used. If used appropriately and regularly, condoms can reduce the risk of developing or transmitting syphilis infection (Peterman and Furness 2015).

9.3.3. SCREENING ON A REGULAR BASIS

This includes testing individuals who are at a high risk of developing syphilis regularly such as every three to six months depending on their level of exposure and behavior. Asymptomatic or infections that are latent that may go undetected and mistreated could potentially be found by screening (Peterman and Furness 2015).

9.3.4. EDUCATION OF HEALTH PROFESSIONALS

This includes providing current knowledge and training on the recognition, treatment, and avoidance of syphilis to medical professionals, laboratory workers, and public health personnel. Education can create awareness and encourage adherence to policies while further improving the standard and range of syphilis care (Peterman and Furness 2015; Lazarini and Barbosa 2017).

9.3.5. PERFORMING DIAGNOSTIC TESTS

This means improving the availability and affordability of syphilis testing services, particularly for high-risk populations including pregnant women, MSM, sex workers, and HIV-positive individuals. Testing can help in early syphilis finding, treatment, and preventing the disease's spread (Peterman and Furness 2015).

10. CONCLUSION

Antibiotic resistance in syphilis is a major public health issue that makes treatment and management difficult. *Treponema pallidum* is the bacterium that causes the several phases of syphilis, which can have major health effects if untreated. Lesions and rashes are present throughout the primary and secondary stages, however other tissues and organs may be affected at the tertiary stage. Syphilis is primarily treated with antibiotics, mainly benzathine penicillin G. Treatment choices are currently being hampered by the development of antibiotic resistance, particularly in vulnerable groups like HIV patients, pregnant women, and men who have sex with men. It is especially important to be aware of the resistance to tetracycline and macrolides, which are frequently used as alternatives for people allergic to penicillin. Finding out if syphilis is resistant to treatments is really important for controlling and managing the disease. But there are several things that make it difficult to accurately assess resistance, such as not enough data, difficulties in growing the bacterium in a laboratory, no standardized ways to test for resistance, and limited access to advanced techniques for studying the bacteria at a molecular level. To address these problems, healthcare providers, researchers, and policymakers need to work together to improve surveillance systems, make testing methods uniform, and enhance access to new technologies. By finding solutions to these difficulties, we can have a better understanding of and fight against antibiotic resistance in syphilis. This will ultimately help improve the outcomes of treatment and overall public health. Antimicrobial resistance in syphilis is being identified using new techniques. By using these techniques, we can improve therapy options while learning more about how resistance functions. We can discover crucial details about the genes of T using molecule-sequencing methods like whole-genome sequencing, PCR tests, and next-generation sequencing. Pallidum is the name of a particular region of the brain. Resistance mechanisms refer to the body's defenses against injury or means of combating noxious substances. Other approaches to diagnosing and treating syphilis are under investigation. These consist of metagenomic sequencing, digital PCR, mass spectrometry, microfluidic tests, and machine learning.

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