REVIEW PAPER

ISSN: 0331 - 670X

https://doi.org/10.51412/psnnjp.2024.04

The Nigerian Journal of PHARMACY
AS MEN OF HONOUR WE JOIN HANDS
THE OFFICIAL ORGAN OF THE PHARMACEUTICAL SOCIETY OF NIGERIA FOUNDED 1927

# Effect of Antimicrobial Resistance in the Treatment of Sexually Transmitted Infections

Asumah M. Onyeka[1*], Chiamaka B. Agbaetuo[2], Kenechukwu E.A. Ujam[3], Fadilulahi A.Usman[4], Augustine O. Odibo[5], Chika B. Ojumah[6], Olabanjo B. Oladoyin[7], Adedoyin E.Daramola[8]

[1]Department of Pharmaceutical Chemistry, Madonna University, Elele, Rivers State, Nigeria.
[2] Department of Clinical Pharmacy, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.
[3]Servier Pharmaceutical Development ltd, Lagos, Nigeria. [4]Department of Molecular Biology and Biotechnology, Nigerian Institute of Medical Research, Yaba, Lagos, Nigeria.
[5]Department of Pharmaceutical Chemistry, University of Benin, Benin City, Nigeria.
[6]Department of Pharmaceutical Microbiology, Delta State University, Abraka, Nigeria.
[7]Department of Pharmacology and Toxicology, Kaduna State University, Kaduna, Nigeria.
[8]Department of Biology, University of Benin, Benin City, Nigeria

ARTICLE INFO

*Article history:*

Received 15 August 2023
Revised 14 October 2023
Accepted 29 December 2023
Online Published 30 April 2024

*Keywords:*

Sexually transmitted infections,
antimicrobial resistance,
antimicrobial stewardship,
cost of antimicrobials

*Corresponding Author:
Asumah, M., Onyeka
Email address: asumahyeka@gmail.com
Phone Number: +2349030948226
https://orcid.org/0009-0000-1538-2353

ABSTRACT

**Background:** Sexually transmitted infections (STDs) are hyperendemic in many developing countries where the diagnostic tools and treatment are usually poor. The constant abuse and misuse of antimicrobials have contributed to the emergence and spread of antimicrobial resistance (AMR) in the treatment of STIs. In this review, we looked broadly at the epidemiology of STIs, causative factors, surveillance reports on AMR, and antimicrobial stewardship, among others.

**Methods:** Using pertinent keywords like "antimicrobial resistance", "sexually transmitted infections", "treatment effectiveness", and similar terms, the databases of Google Scholar, PubMed, Embase, and the Cochrane Library were searched.

**Conclusion:** Antimicrobial stewardship implementation is important for the reduction of antimicrobial resistance. In the treatment of sexually transmitted infections, antimicrobial resistance has made it hard with increased morbidity and recurrence. The prevalence of STI's and AMR can be reduced through proper sensitization and health professionals ensuring that antibiotics are used at the right time, for the right indication, right dose and right dosage form.

## 1. Introduction

Antimicrobial resistance (AMR) is a health crisis affecting the treatment of many infections, especially sexually transmitted infections (STIs)[1]. Antimicrobial susceptibility studies done on samples isolated from sputum, urine, and vaginal swab collected from two major cities in Nigeria showed the presence of single or multidrug resistance by most of the pathogens[2]. According to the World Health Organization (WHO), the major driving force of antibiotic resistance is abuse of antibiotics. Contracting infections that are resistant to antimicrobial agents can result in severe illnesses, extended hospital stays, escalated healthcare expenditures, elevated costs associated with using alternative, more potent drugs, and a heightened risk of treatment not achieving its intended effectiveness[3]. AMR also affects the general cost of healthcare. The Centre for

Disease Control records that AMR costs the United States $55 billion yearly from healthcare costs and reduced productivity due to illness[4]. It is important to understand the impact of antimicrobial resistance on the treatment of sexually transmitted infections (STIs) and put measures in place to prevent and curtail the growing risk this poses to patients' health. There has been an observable upward trend in the cost of antibiotics and antibiotics that used to work five years ago for certain infections can no longer be used in recent times due to resistance. This questions if these drugs now being used in the treatment of sexually transmitted infections will remain effective if antimicrobial resistance is not controlled. One essential strategy in managing antimicrobial use to prevent antibiotic resistance is known as antimicrobial stewardship. Antimicrobial stewardship involves a comprehensive, collaborative approach aimed at selecting the most suitable medications for eligible patients and ensuring their appropriate use over the prescribed duration. The primary goal is to mitigate the potential for the development of antibiotic resistance[5]. This involves setting up educational programs to inform health professionals and the public about the safe and best ways to use antibiotics. This ensures that the right dose, right drug, and right duration for the right indication are practiced in the prescription and use of antibiotics. In this review, we look at the causes of antimicrobial resistance, the cost of therapy, and even the application of antimicrobial stewardship in the prevention of antimicrobial resistance.

### 1.1 Epidemiology of STI

Sexually transmitted infections (STIs) are an important global health concern as more than 1 million people are newly infected with the four most curable STIs each day *Treponema pallidum*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Chlamydia trachomatis* [6-8]. This burden has been disproportionately high among low- and middle-income countries, and African countries account for 20% of all STIs with an estimated prevalence of 12% for trichomoniasis, 4% for gonorrhea, 2% for chlamydia, and 1.5% for syphilis in the general population[9]. STIs are often asymptomatic, and when there are symptoms, they have transmitted infections (STIs), have been recognized as often not specific. For example, estimates indicate major public health problems for a few years. 70-75% of women infected with Chlamydia trachomatis are symptom-free[10]. Despite sensitization for behavior change to key populations for STIs and HIV, the number of STIs is still increasing in different African countries. Therefore, other measures, such as systematic screening, testing, and treatment for most at-risk populations and their partners, are still needed for better management of this burden[11]. A meta-analysis published in 2018 has shown that in West African regions, among women, higher-risk populations such as sex workers had a higher prevalence of Gonorrhea and syphilis than clinic/community-based populations[12]. Factors associated with the acquisition of STIs include lack of STI prevention information, having multiple sexual partners, and inconsistent use of condoms[13-15]. As some STIs are asymptomatic STI prevalence is usually underestimated, and many patients seek treatment at the late stages of infection, which may contribute to irreversible complications[16]. Late diagnosis is not only due to asymptomatic STIs but also due to stigmatization at health facilities, and so many patients self-medicate at home[17]. Timely diagnosis and treatment of STIs are often hampered by the lack of symptoms, inadequate and/or poor availability of diagnostics, and inaccessibility and low quality of treatment in resource-limited settings[18]. As data on STI burden are critical to guide STI prevention and control activities, the first strategic direction of the Global Strategy for STI Prevention and Control is to increase information, including STI prevalence estimates, for focused public health action. The 2019–2020 Nigerian Demographic Health Survey (RDHS) estimated that about 4.4% of the general population between 15–49 years old reported having at least one STI symptom during the last 12 months before the survey[19].

Despite the result, report-based STI surveillance systems tend to lead to medical advances, STIs continue to pose a threat to the underestimation of the total number of new health and welfare of individuals. The correctness of the incidence rate is determined by the accuracy and completeness of case reporting. The most comprehensive data on incidence comes from a few industrialized countries. Sexually transmitted infections are hyperendemic in many developing countries, including their rural areas where the facilities for diagnosis and treatment are usually inadequate.

### 1.2 Causative Factors of Antimicrobial Resistance (AMR) in Sexually Transmitted Infections (STIs)

There is a growing global menace of the emergence of multidrug-resistant sexually transmitted infections. There are possible causes for this phenomenon that have been identified by studies done in the past decade. The discussion on the causative factors of AMR in STIs will be under the following subsections:

### 1.3 Patients

The "patients" category has a direct impact on this growing AMR threat in effectively treating STIs as many of their practices contribute to this menace. Despite the justified and appropriate use of antimicrobials contributing to AMR, many patients self-medicate on antimicrobials and as such they take them at low/excessive doses, at the wrong dosing frequency, and the wrong duration of therapy[20]. Subsequently, it contributes to the development and spread of antimicrobial resistance. This misuse/abuse of antimicrobials is facilitated by the unregulated drug distribution channels and ease of access to the antimicrobials without a prescription issued by qualified health personnel. Reports showed that patients tend to skip/miss doses once they start feeling better and the symptoms have subsided[21]. It was also reported that some patients abandoned their drugs when they experienced side effects which in turn resulted in a relapse of the infection with more terrible symptoms caused by an extensively resistant strain of the microorganism[21].

### 1.4 Drug Circulation, Quality, and Regulations

The drug distribution channels are porous as the regulations surrounding the circulation of antimicrobials are loose. There is an ease of accessibility to antimicrobials without a duly signed prescription in most patent medicine stores as well as pharmacies, particularly in developing countries. In Africa, drug hawkers with little to no adequate knowledge about the tenets of antimicrobial use, sell a cocktail of antimicrobials to individuals for their monetary gains while wreaking havoc on the unsuspecting populace. In addition, research showed that antimicrobials circulated in Africa are of substandard quality[21]. When the quality of the antimicrobial is uncertain, patients will not be getting the right drug, at the right dose, in the right status, and in the right dosage form. Consequently, a patient may be getting a sub-therapeutic or toxic dose of the antimicrobial which contributes to AMR. There may also be fake/counterfeit antimicrobial where the drug does not contain any antimicrobial or contain a wrong pharmaceutical ingredient[21].

### 1.5 Healthcare Providers

Clinicians are responsible for prescribing antimicrobials for treating STIs and their prescribing pattern varies. There have been reported incidences of inappropriate antimicrobial prescriptions which featured the wrong drug, incorrect doses, and unnecessary antimicrobial therapy[21]. In a study carried out by Saleh et al.[22], it was shown that 63.7% of the clinicians prescribed antibiotics with the wrong duration of treatment while more than 50% of cases had inappropriate prescription doses[21]. Usually, the clinicians begin with an empiric treatment using a broad spectrum antimicrobial pending the time results of the antimicrobial susceptibility testing will be ready. Unlike the narrow-spectrum antimicrobial that eliminates the pathogen-causing disease, a broad-spectrum antimicrobial agent, in addition to eradicating the pathogens, also disrupts the normal flora in the body[21]. Hence, this practice contributes to the growing resistance to antimicrobials.

### 1.6 Non-human Use of Antimicrobials

The use of antimicrobials in treating and preventing infections in animals has been a common practice. This can result in the development of resistant strains of microorganisms which are passed onto humans upon direct consumption of meat obtained from the animal or a product of the animal. The spread can also be environmental where fecal matter or urinary waste of the animal gets into water sources for humans[21]. In addition, plants are often sprayed with manure that has been mixed with antibiotics to prevent infections. It is imperative to recognize that there is a selection pressure that promotes the viability of resistant microbial strains when antimicrobials are used in agriculture[21].

## 2. Application of Antibiotic Stewardship in the Treatment of STI

A major worldwide health issue, antibiotic resistance results from the improper use of antibiotics, which raises morbidity and mortality rates[24]. One of the measures that must be used in regular antimicrobial use to prevent antibiotic resistance is antimicrobial stewardship. Antimicrobial stewardship is an integrated, multidisciplinary approach that is used to choose acceptable medications for suitable patients for an appropriate period to reduce the risk of the emergence of antibiotic resistance[24]. The primary objective of antimicrobial stewardship is to prevent microbial Resistance; by implementing its tenets in the treatment of microbial infections, it can assist in lessening failed therapies, such as those associated with the majority of STI treatments, which can, in turn, contribute to microbial resistance. Treatment for sexually transmitted infections should follow certain antimicrobial stewardship standards. These guidelines are based on the five Ds: right drug, correct dose, right drug route, appropriate duration, and timely pathogen-directed treatment used to de-escalate[24].

To make an accurate diagnosis and to make sure that these rules are being followed, prescribers and other medical experts play a crucial role. It is encouraging that so many organizations have begun implementing antimicrobial stewardship programs in acute care settings to encourage the responsible use of antibiotics and prevent potential side effects.

The U.S. National Action Plan released a five-year plan in 2015 to lower antibiotic resistance by promoting the development of innovative preventative measures, improving surveillance, and implementing evidence-based antimicrobial stewardship practices[25]. The number of needless antimicrobial prescriptions has decreased from 25.6% to 17.4% in the emergency department since the implementation of antimicrobial stewardship[26]. Even before antibiotic resistance emerged, improper antibiotic prescribing led to a more significant number of deaths from infections that were easily treatable and curable. Azithromycin and ceftriaxone are the most commonly used treatments for sexually transmitted infections like gonorrhea, but because of antimicrobial resistance, Gonorrhea is becoming increasingly difficult to treat and is now classified by the CDC as an "urgent threat" because of how frequently it can spread due to antibiotic resistance[27,28]. To increase their knowledge of infectious diseases and boost their confidence in prescribing antibiotics, health professionals should be encouraged to enroll in continuing education courses[29] on antibiotic stewardship. This should be included in undergraduate medical education as well because it will enhance the usage of antibiotics and have benefits in the future[30].

### 2.1 Sexually transmitted infections Resistance Monitoring Effect

Antimicrobial resistance monitoring is a critical component of the global strategy of WHO to combat sexually transmitted infectionss because reliable data is necessary to contribute to the improvement of global guidelines used in national clinical management, building public health policies, and assessing the effectiveness of prevention and control strategies[31,32]. In 2018, the WHO recommended two data collection systems, the UNAIDS Global AIDS Monitoring (GAM) system and the Gonococcal Antimicrobial Surveillance Programme (GASP) for AMR monitoring in specific sexually transmitted diseases at national levels worldwide, which are a part of the eight diseases that pose a threat to reproductive and sexual health and are responsible for the tremendous burden of STI globally[35]. Although there are over 30 microbial parasites that cause STIs, these eight are linked to the highest number of incidents. Four of these are curable: gonorrhea, syphilis, chlamydia, and trichomoniasis, while the others are incurable; hepatitis B, herpes simplex (HSV), human immunodeficiency virus (HIV), and human papillomavirus (HPV)[32,33].

High AMR levels can make treatment challenging or even incurable in the worst-case scenario, especially in gonorrhea infections. The first strain of ceftriaxone-resistant gonococcal isolates was found in 2009 and has become widespread, especially due to sexual activities during international travel[34]. Drug-resistant gonococcal strains have since been on an increasing trend. Antimicrobial Resistance in *N. gonorrhoeae* is reported by 70% of countries, with 88% of nations conducting STI surveillance and 64% of countries monitoring antibiotic resistance, which shows that there is a growing effort to combat STIs[36]. AMR testing is limited in some developing countries because they rely on the symptomatic diagnosis of Gonorrhea over laboratory testing of specimens, while in some developed countries, the use of molecular methods of diagnosis reduces the chances of AMR testing and ultimately hinders AMR monitoring[37].

The Western Pacific region has witnessed an increasing level of Resistance to ceftriaxone, azithromycin, cefixime, and ciprofloxacin, according to WHO[31]. There has equally been an increasing prevalence of Resistance to these antibiotics in Africa and around the world over the years, but one issue of concern is the use of ciprofloxacin in the treatment of STIs, specifically gonorrhea, although the Center for Disease Control and Prevention recommendations have eliminated the use of fluoroquinolones for empirical treatment of gonococcal infections since 2006[34,38].

There is an urgent need for new methods that can reduce the prevalence and spread of drug-resistant STIs; studies of new antimicrobial drugs and vaccines should be encouraged[39]. Several attempts to produce vaccines for combating drug-resistant gonococcal strains have proved futile; however, with the advent of bioinformatic tools and computational methods, which have made the identification and characterization of antigens much easier, there may be light at the end of the tunnel in time to come[40]. As the number of drug-resistant STIs rises worldwide, countries should develop long-term monitoring systems

and actively seek ways to strengthen their policies, create action and response plans[33], and encourage healthcare practitioners to follow guidelines put in place by governing health organizations like the World Health Organization and the Center for Disease Control.

### 2.2 Treatment of Antibiotic-Resistant STI

The growing occurrence of antibiotic-resistant bacteria, together with the fast pace at which newly synthesized drugs develop resistance, has shifted to the use of antimicrobials from complementary and alternative medicine. Antimicrobials of plant origins, such as essential oils, are being researched and are part of existing therapies that are active against certain forms of bacteria implicated in sexually transmitted infections (STIs)[42]. Essential oils such as cinnamon, thyme, and clove oil have shown promising properties against 9 strains of *Haemophilus ducreyi*, the organism implicated in genital ulcers. Some cases of *N. gonorrhoeae* were being managed with eucalyptus oil and have shown positive results[43]. The use of non-antimicrobial products such as probiotics, although controversial, has been shown by some studies to be effective in the treatment of bacterial vaginal infections that are recurrent and resistant to antibiotics when used in conjunction with antibiotic therapy[44]. Current treatment guidelines have been updated to match the growing resistance. An example of this is in the treatment of Gonorrhea, where due to the increasing resistance to azithromycin, a part of first-line empirical treatment, the CDC guideline has omitted it from the current guideline. This update now states a monotherapy of ceftriaxone and doxycycline would be added if there is a case of co-infection with Chlamydia (2020). Newer studies are probing towards the development of antimicrobial peptides (AMP) expressed in innate vaginal immunity as an alternative therapy to antibiotic-resistant STIs[45]. AMPs being from self, are harmless and have less likelihood of developing resistance[8]. Studies have identified the polypeptide LL-37 as a potent AMP with antimicrobial activities against a range of bacteria such as *Staphylococcus aureus*, *Chlamydia trachomatis*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, which are implicated in STIs[46]. The shortcomings of AMPs lie in the expensive and cumbersome methods of production; however, the silico analysis method shows promising ways to counter it. The current treatment options for antibiotic-resistant STIs focus more on the use of novel synthetic antimicrobials, plant-based antibacterials, and non-antimicrobial products. Further research is being carried out on newer therapy options, such as antimicrobial peptides.

### 2.3 Cost of Therapy in the Antimicrobial Treatment of STIs

Although antimicrobial resistance is natural, the misuse of antimicrobial agents has greatly accelerated the development of resistance[41]. This misuse of antibiotics could also be possible under usage, known as lack of compliance. This can sometimes be significantly affected by the cost of the treatment. Studies should be carried out to find out the relationship between cost of therapy and adherence. Are patients more likely to take their drugs completely if they are more expensive? or would it deter them from getting the drug in the first place?.

## 3. Discussion

According to the World Health Organization, there are an estimated 1 million new cases of STIs every day around the world[1]. There are over one million new cases of chlamydia, gonorrhea, syphilis, and trichomoniasis every day[1]. These STIs can have serious health consequences if left untreated, including pelvic inflammatory disease, infertility, and even death[12]. The two most commonly used antibiotics for treating STIs are azithromycin and tetracycline[10], Both azithromycin and tetracycline can be rendered ineffective if the bacteria develop resistance to them. One of the multitude of strategies for the development of resistance is through mutations in the genes that code for the proteins that the antibiotics bind to. If mutation occurs in these genes, the antibiotics cannot bind to the ribosomes, and they are no longer effective. Another mechanism is through the production of enzymes that break down the antibiotics before they can work. There are a few different factors that can contribute to antibiotic resistance in STI-causing bacteria. One major factor is the overuse of antibiotics. When antibiotics are used too often, it gives the bacteria more opportunities to develop resistance. Additionally, poor infection control practices in healthcare settings can lead to the spread of antibiotic-resistant bacteria[12]. Consequently, the relevance of antimicrobial stewardship cannot be over-emphasized and it is a set of principles and practices that help ensure the appropriate use of antimicrobial agents. In the context of STI treatment, antimicrobial stewardship includes only prescribing antibiotics when they are needed, choosing the right antibiotic for the specific infection, and using the lowest effective dose, among others. Antimicrobial stewardship can help prevent the development of antimicrobial resistance and improve treatment outcomes for people with

STIs[1]. There are a few different strategies that can be used to implement antibiotic stewardship in the treatment of STIs. One strategy is education and training, which involves educating healthcare providers and patients about antibiotic resistance and proper antibiotic use. Another strategy is surveillance, which involves monitoring antibiotic use and resistance patterns to identify potential problems and target interventions. Finally, there is infection control, which includes practices like hand hygiene and environmental cleaning to reduce the spread of antibiotic-resistant bacteria. The cost of therapy is another important consideration when it comes to antibiotic stewardship in STI treatment. The cost of antibiotics can vary greatly, and it is important to choose a cost-effective option that will still be effective in treating the infection. Additionally, the cost of treating antibiotic-resistant infections can be much higher than treating non-resistant infections, so it is important to consider the potential cost savings of effective antibiotic stewardship.

## 4. Conclusion

Generally, educating patients about prudent antimicrobial use and antimicrobial resistance; regulating the circulation/distribution of antimicrobials; continuously mandating health professionals to learn about antimicrobial resistance, importance of adherence, microbial screening; and limiting the use of antimicrobials in livestock and farm produce. All these will considerably decrease the emergence and spread of antimicrobial-resistant strains in the treatment of sexually transmitted infections as well as prolong the timeframe of antimicrobial efficacy and effectiveness in recent times. It is also important to educate the public on safe sex measures and reduce the prevalence of sexually transmitted infections.


## Acknowledgments

All authors give thanks to Almighty God for making this work a success.


## Conflict of Interest

All authors declared no conflict of interest.


## Funding

No funding was received for this project.


## Authors' Contributions

AMO conceptualized the initial idea and designed the scope and directions of the study. AMO, CBA, KEAU, FAU, AOO, CBO, OBO, and AED made equal contributions to different parts of the review. CBA contributed to the review and managed the references. KEAU designed, retrieved, and analyzed the survey and data obtained from the survey. FAU thoroughly overhauled the manuscript and made valuable inputs. All authors read and edited the final copy of the manuscript. AMO gave the final authorization for the submission of the manuscript.

## References


1. World Health Organization. Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. 2021. Accessed August 15, 2023.
2. Adamu H, Njoku K, Olajide I, Ukponu W, Niyang M (2020) Antimicrobial resistance pattern across two states in Nigeria – A descriptive/observational study. Int J Infect Dis 2020; 101. https://doi.org/10.1016/j.ijid.2020.09.151
3. Dadgostar P. Antimicrobial Resistance: Implications and Costs. *Infect Drug Resist*. 2019; 12: 3903-3910 https://doi.org/10.2147/IDR.S234610
4. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2013; https://doi.org/10.15585/mmwr.rr7004a1es
5. Moody J, Cosgrove SE, Olmsted R, Septimus E, Aureden K, Oriola S, Patel GW, Trivedi KK. Antimicrobial stewardship: a collaborative partnership between infection preventionists and health care epidemiologists. Am J Infect Control. 2012 Mar;40(2):94-5. doi: 10.1016/j.ajic.2012.01.001.
6. World Health Organisation. Sexually transmitted infections (STIs): key facts. WHO (August 2016).
7. World Health Organisation. Report on global sexually transmitted infection surveillance, 2018. WHO Library Cataloguing.
8. World Health Organisation. Global progress report on HIV, viral hepatitis, and sexually transmitted infections. 2021: accountability for the global health sector strategies 2016–2021: actions for impact. 53:1689–99.
9. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, Chico RM, Smolak A, Newman L, Gottlieb S, Thwin SS, Broutet N, Taylor MM. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health

Organ. 2019 Aug 1;97(8):548-562P. doi: 10.2471/BLT.18.228486.
10. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. doi: 10.15585/mmwr.rr7004a1. PMID: 34292926
11. Tapera R, Abotseng D, Mhaka-mutepfa M, Baemedi L, Tumoyagae T. Factors contributing to the upsurge of sexually transmitted infections in Gaborone, Botswana. Med J Zambia. 2019;46(3):197–208. https://doi.org/10.55320/mjz.46.3.558
12. Ohene S, Akoto I. Factors associated with sexually transmitted infections among young ghanaian women. Ghana Med J. 2008 Sep;42(3):96-100. doi: 10.4314/gmj.v42i3.43619. https://doi.org/10.4314/gmj.v42i3.43619
13. Pinto VM, Basso CR, Barros CRDS, Gutierrez EB. Factors associated with sexually transmitted infections: a population based survey in the city of São Paulo, Brazil. Cien Saude Colet. 2018 Jul;23(7):2423-2432. Portuguese, English. doi: 10.1590/1413-81232018237.20602016.
14. Dagnew GW, Asresie MB, Fekadu GA. Factors associated with sexually transmitted infections among sexually active men in Ethiopia. Further analysis of 2016 Ethiopian demographic and health survey data. PLoS One. 2020 May 7;15(5):e0232793. doi: 10.1371/journal.pone.0232793.
15. WHO. World Health Organization. Global health sector strategy on sexually transmitted infections, 2016-2021: Towards ending STIs. WHO/RHR/16.09. Geneva: WHO; 2016; 20(1),58–63.https://www.who.int/publications/i/item/WHO-RHR-16.09 (https://www.who.int/publications/i/item/WHO-RHR-16.09). Accessed August 15, 2023.
16. Nyblade, L., Stockton, M.A., Giger, K. *et al.* Stigma in health facilities: why it matters and how we can change it. *BMC Med* **17**, 25 (2019). https://doi.org/10.1186/s12916-019-1256-2
17. Veldhuijzen NJ, van Steijn M, Nyinawabega J, Kestelyn E, Uwineza M, Vyankandondera J, van de Wijgert JH. Prevalence of sexually transmitted infections, genital symptoms and health-care seeking behaviour among HIV-negative female sex workers in Kigali, Rwanda. Int J STD AIDS. 2013 Feb;24(2):139-43. doi: 10.1177/0956462412472293.
18. World Health Organization. Global health sector strategy on sexually transmitted infections 2016-2021: toward ending STIs 2016:
19. National Population Commission (NPC). Nigeria Demographic Health Survey 2018. The DHS Program ICF Rockville, Maryland, USA, 748. https://dhsprogram.com/publications/publication-fr359-dhs-final-reports.cfm (https://dhsprogram.com/publications/publication-fr359-dhs-final-reports.cfm). Accessed August 15, 2023.
20. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013 Dec;13(12):1057-98. doi: 10.1016/S1473-3099(13)70318-9. Epub 2013 Nov 17. Erratum in: Lancet Infect Dis. 2014 Jan;14(1):11. Erratum in: Lancet Infect Dis. 2014 Mar;14(3):182. https://doi.org/10.1016/S1473-3099(13)70318-9
21. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrob Resist Infect Control. 2017 May 15;6:47. doi: 10.1186/s13756-017-0208-x. https://doi.org/10.1186/s13756-017-0208-x
22. Saleh N, Awada S, Awwad R, Jibai S, Arfoul C, Zaiter L, Dib W, Salameh P. Evaluation of antibiotic prescription in the Lebanese community: a pilot study. Infect Ecol Epidemiol. 2015 Jun 24;5:27094. doi: 10.3402/iee.v5.27094. https://doi.org/10.3402/iee.v5.27094
23. Cosgrove E. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis*. 2006;*42*(Suppl 2):S82–9. 1
24. Dyar OJ, Huttner B, Schouten J, Pulcini C; ESGAP (ESCMID Study Group for Antimicrobial stewardshiP). What is antimicrobial stewardship? Clin Microbiol Infect.

2017 Nov;23(11):793-798. doi: 10.1016/j.cmi.2017.08.026.

25. Centers for Disease Control and Prevention [CDC], National Action Plan for Combating Antibiotic-Resistant Bacteria (National Action Plan). US Department of Health & Human Services; 2015. https://www.cdc.gov/drugresistance/us-activities/national-action-plan.html (https://www.cdc.gov/drugresistance/us-activities/national-action-plan.html) Accessed August 15, 2023

26. Dinh A, Duran C, Davido B, Bouchand F, Deconinck L, Matt M, Sénard O, Guyot C, Levasseur AS, Attal J, Razazi D, Tritz T, Beauchet A, Salomon J, Beaune S, Grenet J. Impact of an antimicrobial stewardship programme to optimize antimicrobial use for outpatients at an emergency department. J Hosp Infect. 2017 Nov;97(3):288-293. doi: 10.1016/j.jhin.2017.07.005.

27. Madanchi H, Shoushtari M, Kashani HH, Sardari S. Antimicrobial peptides of the vaginal innate immunity and their role in the fight against sexually transmitted diseases. New Microbes New Infect. 2019 Dec 10;34:100627. doi: 10.1016/j.nmni.2019.100627. https://doi.org/10.1016/j.nmni.2019.100627.

28. Culver KD, Hicks LM. In silico prediction and mass spectrometric characterization of botanical antimicrobial peptides. Methods Enzymol. 2022;663:157-175. doi: 10.1016/bs.mie.2021.11.002. Epub 2021 Dec 21.

29. Castro-Sánchez E, Drumright LN, Gharbi M, Farrell S, Holmes AH. Mapping Antimicrobial Stewardship in Undergraduate Medical, Dental, Pharmacy, Nursing and Veterinary Education in the United Kingdom. PLoS One. 2016 Feb 29;11(2):e0150056. doi: 10.1371/journal.pone.0150056. https://doi.org/10.1371/journal.pone.0150056

30. Brinkman DJ, Tichelaar J, Graaf S, Otten RHJ, Richir MC, van Agtmael MA. Do final-year medical students have sufficient prescribing competencies? A systematic literature review. Br J Clin Pharmacol. 2018 Apr;84(4):615-635. doi: 10.1111/bcp.13491. Epub 2018 Jan 25 https://doi.org/10.1111/bcp.13491

31. Unemo M, Lahra MM, Escher M, Eremin S, Cole MJ, Galarza P, Ndowa F, Martin I, Dillon JR, Galas M, Ramon-Pardo P, Weinstock H, Wi T. WHO global antimicrobial resistance surveillance for Neisseria gonorrhoeae 2017-18: a retrospective observational study. Lancet Microbe. 2021 Nov;2(11):e627-e636. doi: 10.1016/S2666-5247(21)00171-3. Epub 2021 Sep 2. https://doi.org/10.1016/S2666-5247(21)00171-3

32. World Health Organisation [WHO]. Report on global sexually transmitted infection surveillance, 2018. WHO Library Cataloguing.

33. Weston EJ, Wi T, Papp J. Strengthening Global Surveillance for Antimicrobial Drug-Resistant Neisseria gonorrhoeae through the Enhanced Gonococcal Antimicrobial Surveillance Program. Emerg Infect Dis. 2017 Oct;23(13):S47–52. doi: 10.3201/eid2313.170443. https://doi.org/10.3201/eid2313.170443

34. Tien V, Punjabi C, Holubar MK. Antimicrobial resistance in sexually transmitted infections. J Travel Med. 2020 Feb 3;27(1):taz101. doi: 10.1093/jtm/taz101. . https://doi.org/10.1093/jtm/taz101

35. World Health Organisation. Global progress report on HIV, viral hepatitis, and sexually transmitted infections. 2021: Accountability for the global health sector strategies 2016–2021: Actions for impact. Volume 53:1689–99.

36. St Cyr S, Barbee L, Workowski KA, Bachmann LH, Pham C, Schlanger K, Torrone E, Weinstock H, Kersh EN, Thorpe P. Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020. MMWR Morb Mortal Wkly Rep. 2020 Dec 18;69(50):1911-1916. doi: 10.15585/mmwr.mm6950a6. https://doi.org/10.15585/mmwr.mm6950a6

37. Tapera R, Abotseng, D, et al. Factors contributing to the upsurge of sexually transmitted infections in Gaborone, Botswana. Med J Zambia. 2019. *46*(3):197–208.

38. Kakooza F, Kiggundu R, Mboowa G, Kateete PD, Nsangi OT, Kabahita JM, Ssentalo Bagaya B, Golparian D, Unemo M. Antimicrobial susceptibility surveillance and antimicrobial resistance in *Neisseria gonorrhoeae* in Africa from 2001 to 2020: A mini-review. Front Microbiol. 2023 Apr 6;14:1148817.

https://doi.org/10.3389/fmicb.2023.1148817
39. Riou J, Althaus CL, Allen H, Cole MJ, Grad YH, Heijne JCM, Unemo M, Low N. Projecting the development of antimicrobial resistance in Neisseria gonorrhoeae from antimicrobial surveillance data: a mathematical modelling study. BMC Infect Dis. 2023 Apr 20;23(1):252. doi: 10.1186/s12879-023-08200-4.
40. Maurakis SA, Cornelissen CN. Recent Progress Towards a Gonococcal Vaccine. Front Cell Infect Microbiol. 2022 Apr 11;12:881392. doi: 10.3389/fcimb.2022.881392. https://doi.org/10.3389/fcimb.2022.881392
41. O'Neal P. Antimicrobial resistance: Tackling a crisis for the wealth and health of nations. *Review on Antimicrobial Resistance*, 2014;1: 1–16.
42. Jadimurthy R, Mayegowda SB, Nayak SC, Mohan CD, Rangappa KS. Escaping mechanisms of ESKAPE pathogens from antibiotics and their targeting by natural compounds. Biotechnol Rep (Amst). 2022 Apr 4;34:e00728. https://doi.org/10.1016/j.btre.2022.e00728
43. Ghareeb MA, Habib MR, Mossalem HS et al. Phytochemical analysis of Eucalyptus camaldulensis leaves extracts and testing its antimicrobial and schistosomicidal activities. Bulletin of the National Research Centre 2018:*42*(1), p.16. https://doi.org/10.1186/s42269-018-0017-2
44. van de Wijgert J, Verwijs MC. Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs. BJOG. 2020 Jan;127(2):287-299. doi: 10.1111/1471-0528.15870..
45. Madanchi H, Shoushtari M, Kashani HH, Sardari S. Antimicrobial peptides of the vaginal innate immunity and their role in the fight against sexually transmitted diseases. New Microbes New Infect. 2019 Dec 10;34:100627. doi: 10.1016/j.nmni.2019.100627.,
46. Tanphaichitr N, Srakaew N, Alonzi R, Kiattiburut W, Kongmanas K, Zhi R, Li W, Baker M, Wang G, Hickling D. Potential Use of Antimicrobial Peptides as Vaginal Spermicides/Microbicides. Pharmaceuticals (Basel). 2016 Mar 11;9(1):13. doi: 10.3390/ph9010013. https://doi.org/10.3390/ph9010013