Detection and Characterization of Non-*albicans Candida* inClinical Isolates in Some Healthcare Facilities in Ibadan, Oyo State, Nigeria

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Certification

This is to certify that this Thesis was written by Oluwatosin, A. Odubunmi with Matriculation Number LCU/PG/001069 under my supervision as part of the requirement for the award of Master of Science (M.Sc.) Degree in Medical Microbiology, Department of Biological sciences, Faculty of Natural and Applied Sciences, Lead City University, Ibadan, Oyo state, Nigeria and that this work has not been previously submitted.

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Dedication

This research work is dedicated to the loving memory of my beloved mother-in-law Mrs. Bridget Onaolapo Odumuyiwa (1946-2021).

Acknowledgement

My utmost gratitude goes to Lead City University, Ibadan, Oyo State, my institution of study.

Thanks to the Head of Department, Dr. F.C. Adesina, my supervisor, Associate Professor T.Y. Raheem, Associate Professor B.A. Bamkefa my co-supervisor, and all lecturers. Many thanks to Mr. Alberto Lerner, President and General Manger of CHROMagar™, France for the gift of the novel Chromagar™ Candida Plus used in this research work, also the department of Medical microbiology, Nigerian Institute of Medical Research, Lagos state.

Special thanks to my lovely and adorable wife, Mrs. R. O. Odubunmi, for her supports. Thanks to my parents, Mr. and Mrs. G.E.A Odubunmi.

"I alone stand responsible for the errors, if any, found in the work, not the above-mentioned institutions or persons that assisted in the process of this research work,"

Abstract

Candida species are causes of nosocomial fungal infections and are among the leading causes of hospital-acquired infections. *Candida* infections ranging from superficial infections to highly invasive *Candidiasis* are increasingly being associated with nosocomial infections. Bloodstream infections resulting from *Candida* pathogenic species have high mortality rates. It is considered a public health menace globally. Patient samples were collected and phenotypic identification of *C.auris* and other non-*candida albicans* was done by culture on Sabouraud Dextrose agar supplemented with Chloramphenical. Novel Chromagar^{TM} Candida Plus was also used. GPI protein-encoding genes of the isolates were detected using PCR techniques and primers sequence specific for *C. auris*. A total of 90 *Candida* species were isolated from Adeoyo Maternity Teaching Hospital 42 (46.7%), Ring Road State Hospital 45 (50%) and University College Hospital 3 (3.3%). High vaginal swabs were 39 (43%), Pus/wound swab 31 (34.4%), Ear swabs 11 (12%), Sputum, Endocervical swabs and Urine 3 (3.3%) respectively. This report showed 38.9% (n=35) *C.auris*. *Candida* species detected were *C. krusei, C.famata, C.glabrata* and *C.tropicalis.* A wound swab had a mixed growth of *C.tropicalis, C.famata and C.krusei*. Resistance to fluconazole was detected in all of the isolates with minimum inhibitory concentration of 16µg/mL and 0.03µg/mL, making it a total resistance in this study. There is need for further analysis on the genes responsible for the resistance. Molecular analysis showed 27*C.auris* with 5.8S rDNA having a 134(bp).

Keywords: *Candida* species, Non- *albican candida, C.auris*, Resistance, Polymerase chain reaction (PCR), Minimum inhibitory concentration (MIC)

Word Count: 245

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List of Acronyms

Abbrevation	Full Meaning
NAC	Non-*albicans Candida*
SDA	Sabouraud Dextrose Agar
GPI	Glyco Phosphatidyl Inositol
BSIs	Blood Stream Infections
DNA	Deoxyribonucleic Acid
rDNA	Recombinant DNA
PCR	Polymerase Chain Reaction
qPCR	Quantitative Polymerase Chain Reaction
MALDI-TOF MS	Matrix-Assisted Laser Desorption/Ionization-time of Flight Mass Spectrometry
WGS	Whole-Genome Sequence
SNPs	Single-Nucleotide Polymorphisms
CLSI	Clinical and Laboratory Standards Institute
EUCAST	European Committee on Antimicrobial Susceptibility Testing
MIC	Minimum Inhibitory Concentration
MFS	Major Facilitator Superfamily
ATP	Adenosine Triphosphate
ABC	ATP Binding Cassette
LD	Lanosterol 14-alpha-Demethylase
AMTH	Adeoyo Maternity Teaching Hospital
RRSH	Ring Road State Hospital
UCH	University College Hospital
HIV	Human immunodeficiency virus

Chapter One

Introduction

1.1 Background to the Study

The genus *Candida* contains heterogeneous anamorphic yeasts with about 196-200 species that are physiologically related to ascomycetes or basidiomycetes[1,2]. The name *Candida* was derived from the ancient Rome word, "*candidatus"*, meaning a candidate for public office[2]. Among the important pathogenic species are *Candida albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C.lusitaniae, C. glabrata, C.haemulonii and C. auris.*

The genus *Candida* can be classified as follows:

Phylum: *Deuteromycota*

Class: *Ascomycetes/ Blastomycetes*

Order: *Cryptococcales*

Family: *Cryptococcaceae*

Genus: *Candida*

Candida species are causes of nosocomial fungal infections; they are among the leading causes of hospital-acquired infections[3]. Bloodstream infections resulting from *Candida* pathogenic species have high mortality rates of more than 40%[4]. Among the Candida species, the *C. albicans* is mostly isolated from patient's sample but newly emerging non *C.albicans* species are on the surge currently: *C. parapsilosis*, *C. krusei*, *C.lusitaniae, C. glabrata, C.haemulonii, C. auris* and many more. These *Candida* infections are increasingly being associated with nosocomial infections causing its public health menace globally, from superficial infections to highly invasive *Candidiasis*. The presence of *Candida spp* is identified as part of normal microbial flora of human body:

however, it can be pathogenic at certain conditions thus leading to opportunistic infections in critically ill patients they are said to be the important cause of morbidity and mortality[5,6,7]. The genus *Candida* have been associated with different and numerous clinical manifestations, ranging from highly invasive candidiasis, superficial or mucosa infections, bloodstream infections to intra-abdominal candidiasis[7]. The increased infections owing to *Candida* spp., over the years have been associated with high rate of surgical invasive procedures, the indiscriminate consumption of broad-spectrum antimicrobial agents, and the immune states of critically ill patients[8,9].

C. auris being a new emergent nosocomial *Candida* specie pathogen was reported in 2009 when isolated from the discharge of external ear canal of an adult patient at a Geriatric Hospital in Tokyo[5]. It is a multidrug-resistant pathogen causing outbreaks of invasive infections being associated with healthcare facilities globally[10]. Its association with human contacts or abiotic surfaces aids the ability of this pathogen to cause outbreaks of infection in hospitals. The emergence as a significant pathogen in healthcare facilities is on the increase in cases of candidaemia[11]. *C. auris* is being identified with healthcare-associated person-to-person transmission in many countries[12]. Its transmission is attributed to its ability to adhere to the skin, non-sterile body sites, abiotic surfaces and the invasion of the blood stream. Fungemia resulting from dissemination in the blood stream has been a case in urogenital colonization from urinary catheter[13,14]. This pathogen has the ability and affinity to adhere for weeks on abiotic surfaces and medical equipments in hospitals[15]. Enhanced and enforced infection control in healthcare and down to community settings aids in stopping its transmission.

The phenotypic, chemotaxonomic, and phylogenetic analyses showed affiliations and a close relation to other non-*albican Candida* (NAC) species[11]. The non-*albican candida* species includes *C. haemulonii*, *C. pseudohaemulonii*, *C. glabrata* and *C.tropicalis*,

Candida krusei, *Candida parapsilosis*. The use of conventional identification method in routine diagnostic laboratories often commonly misidentifies *C. auris* as *C. haemulonii* due to close genetic relatedness[16].

C. auris produces smooth cream-colored colonies on Sabouraud Dextrose agar showing negative result to germ tube test. In using CHROMagar™ Candida Plus, *C. auris* produces colonies that show pale cream, having an obvious blue tinge in the surrounding agar after 36 h incubation at 35°C. In microscopy, morphology of cells appears to be ovoid, with no pseudohyphae. It exhibits several phenotypes in different culture conditions, which maybe round-to-oval, elongated[16]. The advanced identification analytical method makes it rapid and accurate in identification[11,17]. Molecular identification of *C. auris* is rapid and accurate by sequencing various genetic loci[14,18]. The molecular identification method will help in combating the misidentifications associated with this fungal pathogen.

Candida auris has emerged globally in hospitals showing its nosocomial tendencies as a multidrug-resistant yeast pathogen with outbreaks of invasive infections. *C. auris* spreads in hospitals through contamination of abiotic surfaces, intensive care medical devices like ventilators, intravenous catheters, and urinary catheterization likewise patient to patient through infected body tissues or fluids causing infections. Attributes' of *C. auris* infection seen in patients gives paucity information and are challenging to interpret owing to its existence in known ill patients. Symptom varies according to its location in the body, an open wound, the blood stream, reproductive system or the ear. A rapid, accurate and specific mycological laboratory analytical method guarantees correct diagnosis of *C. auris*. Early diagnosis of *C. auris* is very remarkable in clinical treatment because it can be life threatening.

The actual prevalence and the epidemiology of *C. auris* is not known, in low income or economic challenged resource limited countries due to little or no research interest shown in definitive identification of this pathogen, coupled with the use of obsolete mycological identification methods. The inadequacy and paucity of data in isolation of *C. auris* owing to challenges in accuracy using conventional diagnostic toolsmakes the epidemiology cumbersome[19]. In the genomic analysis, *C. auris* consists of four known phylogenetically distinct clades, owing to the different geographical regions: clade I (South Asia), clade II (EastAsia), clade III (South Africa), and clade IV (South America)[20]. Clinical samples analyzed in India shows the outbreak of *C. auris* infection from certain periods[21]. In the United Statesand Colombia this emerging multidrug resistant yeast has been isolated[22, 23]. The initial outbreak of *C. auris* in Europe which persisted for long happened in hospital setting[24]. In Israel, Iraq, Oman and United Arab Emirateslikewise in Saudi Arabia *C. auris* has also emerged[25, 26, 27, 28, 29, 30]. In Africa, it was reported of sporadic cases and outbreaks in South Africa, Kenya and recently in Sudan[31, 32, 33].

1.2 Statement of the Problem

The prevalence of *C. auris* is significantly underestimated due to conventional identification methods which does not correctly identify up to the species level thus have the propensity to be missed or misidentified and limits the ability to monitor treatment and track antifungal resistance thus reporting non-*albicans Candida* (NAC) isolates generally as "*Candida* spp." and thereby unknowingly continue to cause outbreaks in Nigeria health care settings. This necessitates medical diagnostic laboratories to routinely identify non-*albicans Candida* isolates to the species level.

1.3 Aim and Objectives of the Study

The General aim of the study was to provide information on *C. auris* and other non-*albicans Candida* as possible cause of superficial or invasive mycosis in clinical setting thus providing data/information for appropriate diagnosis and treatment of non-*albican Candida* (NAC) infections.

The Objectives are to:

i. isolate *Candida* species from clinical samples.
ii. characterize the *candida* into *Candida albicans* and non-*albican Candida* (NAC).
iii. investigate the proportion of *C.auris* and other non-*albican Candida* (NAC) as an etilogic agent in clinical samples in from hospitalized study participants.
iv. determine possible molecular clades of *C. auris* circulating in the study area of Oyo State.
v. assess antifungal susceptibility pattern of the *C auris* against some antifungal drugs like Fluconazole and Amphotericin B.

1.4 Research Questions

i. What is the prevalence of *C.auris*, its molecular identification data in Nigeria?
ii. Has there been phenotypic identification report using CHROMagar™ Candida Plus likewise the routine identification of *Candida* to the species level?

1.5 Significance of the Study

The outbreaks of *Candida auris* and other non-*albican Candida* (NAC) have been reported in hospitals across the globe, findings from this study, will not only give species level identification and distribution, but also defining susceptible or resistant isolates thus giving information on the antifungal susceptibility and enhance epidemiological surveillance. This study will also assess the burden of *C. auris* and other non-*albican*

Candida (NAC) in the study area and provide data on why all non-*albicans candida* should be looked for routinely in clinical samples.

1.6 Scope of the Study

The paucity of information on the emergence, identification and prevalence of *C. auris* in Nigeria mandates this study to identify this emerging multidrug resistance *Candida* among the non-*albicans Candida* isolates to the species level. The challenges in its identification or misidentification using conventional phenotypic methods, requires the application of molecular identification method to provide accurate identification and differentiation of *C. auris* from other yeast in the selected hospitals in Ibadan, Oyo state.

1.7 Limitations of the Study

Some limitation of the study were

1. Industrial strikes by Health professionals
2. Financial constraints
3. Delay in importation of the primers used for molecular techniques.
4. None availability of Echinocandin antifungal susceptibility disc in Nigeria for susceptibility testing which has been the recommended medication in treatment of *C.auris*.

However, all these were overcome and did not significantly hinder the study but only extended the study timeline.

1.8 Operational Definition of Terms

NAC	Non-*albicans Candida*
SDA	Sabouraud Dextrose agar
BSIs	Bloodstream infections
PCR	Polymerase chain reaction

Endnotes

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Chapter Two

Literature Review

2.1 The Genus *Candida*

The genus *Candida* consists of different anamorphic yeasts with species belonging to the class ascomycetes or basidiomycetes[1,2]. The taxonomic classification of Genus *Candida* puts it in the Phylum *Deuteromycota*and Family, *Cryptococcaceae* while its Order is *Cryptococcales*. The obvious truth regarding the cause of nosocomial fungal infections is the thriving menace of *Candida* species; they are among the leading cause of hospital-acquired infections[3]. In bloodstream infections owing to *Candida* pathogenic species, high mortality rates of more than 40%have been reported[4]. In all the *Candida* species, the *C. albicans* is mostly isolated from patient's sample but newly emerging non-*albican Candida* (NAC) species are on the surge currently: *C. parapsilosis*, *C. krusei*, *C.lusitaniae, C. glabrata, C.haemulonii, C. auris* and many more. These *Candida* infections are increasingly being associated with nosocomial infections causing its public health menace globally, from superficial infections to highly invasive *Candidiasis*. The presence of *Candida spp* is identified as part of normal microbial flora of human body:

however, it can be pathogenic at certain conditions thus leading to opportunistic infections, in critically ill patients they are said to be the important cause of morbidity and mortality[5,6,7]. The genus *Candida* have been associated with different and numerous clinical manifestations, ranging from highly invasive candidiasis, superficial or mucosa infections, bloodstream infections to intra-abdominal candidiasis[7]. The increased infections owing to *Candida* spp., over the years have been associated with high rate of surgical invasive procedures, the indiscriminate consumption of broad-spectrum antimicrobial agents, and the immune states of critically ill patients[8,9].

2.2 *Candida auris*: Emerging Multi-Drug Resistant Pathogenic *Candida* Species

Candida auris, a novel non-*albican Candida* specie, was first isolated in 2009 from the ear canal of a Japanese patient in a Geriatric hospital in Tokyo, the name *"auris"*, means "ear" in latin word: it is an emerging multi-drug resistant fungal pathogen that has been isolated on five continents[5]. *Candida auris* has emerged to cause outbreaks of infection from minor cases of superficial to highly invasive bloodstream infections, diseases in immune compromised individuals and in healthcare facilities around the world. Its association with human contacts or abiotic surfaces aids the ability of this pathogen to cause outbreaks of infection critically ill patients in hospitals with high mortality rates of about 72%[10,11]. The awareness of its emergence as a significant pathogen in healthcare facilities is on the increase in cases of candidaemia[12]. The phenotypic, chemotaxonomic, and phylogenetic analyses showed affiliations and a close relation to other non-*albicans Candida* species: *C. parapsilosis*, *C. krusei*, *C. famata*, *C.lusitaniae, C. glabrata, C.haemulonii, C. auris* and many more [12]. The use of conventional identification method in routine diagnostic laboratories often commonly misidentifies *C. auris* as *C. haemulonii, C. famata*due to close genetic relatedness[13]. *Candida auris* infection

symptoms are non-specific; making it cumbersome in differentiating between other forms of systemic infections[13].

2.2.1 How *C.auris* and other Non-*albican Candida* (NAC) Spreads

Transmission of *C. auris* and other non-*albican Candida* (NAC) is driven by ability to invade the bloodstream, colonize the skin, catheters and non-sterile body parts[14, 15]. It possess the ability to adhere and persist for long periods on abiotic surfaces, including dry and moist surfaces, bedding materials, floors, sinks, beds and equipments in health care facilities[16,17]. *C. auris* has been isolated from other body sites or specimens which include the nose, external ear canals, urine, wounds, and rectum[17]. Risk factors for *C. auris* bloodstream infections (BSIs) includes major surgical procedures, diabetes, prolong use of broad-spectrum antibiotics, long-term hospitalizations, patients using medical devices such as ventilators, feeding tubes, and central venous catheters[18]. Screening for *C. auris* is commonly done using a composite swab of the patient's axilla and groin regions, as these sites have been determined to be high-yielding and consistent sites of colonization[14,16]. In *C. auris*, infections can occur in patients' of all ages, but most infections have been reported in adults[19].

2.2.2 Morphological Identification of Non-*albican Candida* (NAC)

Candida auris

In Medical diagnostic laboratories, definite identification of Candida species can be cumbersome when relying on phenotypic or biochemical characteristics because of inaccurate identifications in species. There are many fungal identification methods that can be used to detect *C. auris*[20]. *Candida auris* has been identified among ascomycetous fungus in the genus *Candida*. The *Candida auris* isolates on Sabouraud dextrose agar appears as colonies of smoothly white to cream-colour after 48 hours of incubation at 36°C, on CHROMagar™ Candida Plus, it appears as rarely beige or pale cream to white

colonies with a distinctive faint to strong blue halos in the surrounding agar after 36 hours of incubation at 36°C. CHROMagar™ Candida Plus is a novel and distinct chromogenic media which is selective and differential in differentiating *C. auris* among other *Candida* species. This is based on color production, making it superior to commonly used mycological media couple with its ability to selectively inhibit bacterial growth[21]. This media is easy to use and rapid in identification of *C. auris* and no need for professional expertise as *C. auris*[22]. The conventional phenotypic methods used in detecting and identifying *Candida auris* are tedious, and lack the necessary cogency (sensitivity and specificity). Therefore, in ascertaining the correct identification of *C. auris*, reliable identification methods such as rDNA sequencing, *C. auris*-specific PCR/qPCR, or MALDI-TOF MS should be further explored[20].

2.3 Epidemiology of *C.auris*

Since its first isolation, a research conducted detailed on the initial misidentification of *C. auris* as *C.haemulonii* in South Korea, 1996[5,23]. This means that *C. auris* has been in existence before the initial isolation in 2009. Genomic analysis proofs that *C. auris* has been in existence far back as 360 years ago and around 38 years ago for different *C. auris* subclades[24]. Infections associated with *C. auris* have been reported globally, in South Africa, Europe, and America[25, 26, 27, 28, 29, 27]. Its emergence have been reported from South Korea, Russia, China[30,19]. In India, the first outbreak of *C.auris* infection was reported in 2013[31]. In Africa, the first identification of sporadic cases and outbreaks were reported in South Africa, Kenyain East Africa and a recent report in 2019 from Sudan[25, 32, 33]. In Nigeria, clinical laboratory confirmed isolates, sporadic cases or nosocomial outbreaks of *C. auris* have not been reported owing to challenges in its identification or misidentification using conventional phenotypic methods thereby having no

epidemiological report. This will be the first comprehensive study on the emergence of this multidrug-resistant yeast, *C. auris* from Nigeria and West Africa.

2.3.1 Genomic Epidemiology

Whole-genome sequence (WGS) analysis were used to distinguish *C. auris* into four phylogenetically discrete genetic clades: the South Asia Clade (I), the East Asia Clade (II), the SouthAfrica Clade (III), and the South America Clade (IV)[24]. These clades are strongly associated with different geographic regions differentiating each clade by tens of thousands of single-nucleotide polymorphisms (SNPs), while the genetic diversity within a clade is extremely low[34]. The East Asian clade appears to infect the ear only, whereas the other clades are known to cause invasive infections, nosocomial transmission and health-care outbreaks[35]. In advent of globalization and international travel, it is essential to note that without a definitive origin or a comprehensive evolutionary analysis, geographic distribution could be attributed to importation or local spread therefore reflecting the origin of a clade[10]. A new *C. auris* clade representing Clade V, was reported in Iran; having 200,000 SNPs more than other known clades[36]. The representative of a fifth clade from Iran was from a 14 year old girl patient diagnosed of otomycosis with no travel history[37]. This suggests that this isolate has been in existence and not a recent *C. auris* introduction into the country[37]. In the United States, infections owing to all four clades have been identified but the current epidemic is dominated by clade I and clade IV[38]. In regards to travel-related epidemiological links, eight clinical cases have been attributed to it, an indication that initial travel-related cases made-up the U.S. *C. auris* population while clades I and III predominate in European outbreaks studied[39].

2.4 Biology of *Candida auris* and other Non-*albican Candida* (NAC)

C. auris and other pathogenic *Candida* species such as *C. albicans*, *C. tropicalis*, *C. parapsilosis*, can translate the CTG codon into serine instead of leucine[40]. *C. auris* like other *Candida* species can form biofilms undergo filamentation, and morphological transitions[23, 26, 41, 42, 43]. The adaptation of *C. auris* to environmental stresses can make it grow at high temperatures >40˚C likewise tolerance to high salt concentrations unlike its closely related species[19]. *C. auris* can survive several weeks on environmental surfaces, colonize human skin likewise tolerance to some commonly used disinfectants giving way for nosocomial infection[24]. *Candida auris* do exhibit several morphological phenotypes which is a common trait in pathogenic *Candida* species[19]. In colony phenotypic switching, *C. auris* transits morphologically between pink, white, and dark purple colony phenotypes when cultured on CHROMagar[44]. In *C. auris*, it is unclear if the colony phenotypic switch is heritable and whether it is associated with virulence and/or antifungal resistance[24]. In fungal invasion of host tissues, the hyphal or pseudohyphal cell growth in pathogenic *Candida* species has a crucial role to play[45, 46]. Under specific conditions, *C. auris*forms true hyphae while its thermotolerance and osmotoleranceare used as distinguishing characteristics from other yeasts[24]. These characteristics: thermotolerance and osmotolerance makes this pathogen persistent and survives on biotic and abiotic surfaces for extensive periods[47,48,49].

There are differences and variations among *C. auris* isolates likewise the in clades formation of biofilm[42]. These biofilms are known to be structural microbial communities formed on abiotic or biotic surfaces which are embedded in extracellular matrix[50]. The biofilms developed on surfaces by *C. auris* are weak when compared with biofilms formed by *C. albicans*[23]. Biofilms in *C. auris* aids resistance in antifungal agents being used likewise its virulence thus aiding its transmission. It is paramount to directing

resources into novel therapeutics approaches which targets biofilms formation in *C. auris* as this will help in combating the global menace *C. auris* causes in public health.

2.5 *Candida auris* and other Non-*albican Candida* (NAC) are Menace in Nosocomial Infections Thriving Globally among Hospitals

The interwoven relationship between host, pathogen and the environment paves way for the thriving and transmission of *C. auris* locally and globally. The exposure of individuals, health workers inclusive during outbreaks or sporadic cases in hospital environments facilitates transmission of this *candida* spp with local spread by surviving on inanimate objects and international travels. The ability of *C. auris* to thrive lies on evading desiccation likewise resistance to peracetic acid, quaternary ammonium compound disinfectants and concentrations of sodium hypochlorite[51, 52, 53]. A full scale investigation is essential in sporadic cases[51, 54]. In developing countries having healthcare challenges, indiscriminate antimicrobial usage couple with vulnerable population is building sites for thriving of *C.auris* in the past decades. The emanation of different *C.auris* clades across the globe could result in a hospital circulation of strains having different mating type as a result of genetic amalgamation, which could lead to genetic variegation, shuffling of drug resistant alleles, evolution of new resistance and virulence mechanisms which can speed up its spread globally[55].

C.haemulonii

The first clinical isolation of this fungus from a human was reported in 1984 from the blood of a patient with renal failure[56]. It has also been isolated from toe ulcers and the nails of diabetic patients[57]. In 1986, a case was of *C. haemulonii* fungemia was reported from a patient with cancer[58]. Two genetically distinct *C. haemulonii*groups, I and II renamed as *C. haemulonii* and *C. duobushaemulonii* respectively were described from *Candida haemulonii* complex of different geographic originsand clinical sources[59]. There

were reports that showed that *C. haemulonii* is susceptible to echinocandins such as caspofunginor micafungin[60,61]. However, it is not certain that echinocandins or voriconazole are actually efficacious in the treatment of *C. haemulonii* candidemia[62]. Biofilm production is crucial for the development of broad spectrum of infections in the host. It is also useful for defending pathogens from invasion and in the development of antifungal resistance; biofilms display lower susceptibility against antifungals, including caspofungin, micafungin and amphotericin B[63, 64].

C. parapsilosis

There have been increases in the incidence of *C. parapsilosis* fungemia in more than two decades, which has been associated with cause of candidemia in Asia, Europe and Latin America healthcare facilities[65]. The transmission of *C. parapsilosis* can be as a direct transmission causing invasive disease in patients with no previous colonization which resulted from contact with healthcare workers' being colonized[66]. In forming biofilms, *C. parapsilosis* colonizes medical devices, abiotic surfaces for more than 2 weeks thus causing nosocomial outbreaks[66, 67]. *C. parapsilosis* has emerged to be the biggest biofilm producer among *Candida* species after *C. albicans*[68]. Higher mortality rates have been associated with *C. parapsilosis* Candidemia with isolates forming biofilm[69, 70].

C. krusei

In finding out the increase in cases of Candidemias caused by *Candida* spps, *C. krusei* has been identified as an emerging pathogen frequent in cases of acute leukemia[71]. The prophylactic use of antifungals has been associated with invasive infections or colonization with *C. krusei*[72, 73].

This has made *Candida krusei* to be known as a potential multidrug-resistant (MDR) fungal pathogen, owing to the intrinsic fluconazole resistance including decreased susceptibility to both flucytosine and amphotericin B[71,74,75,76,77,78,79,80].

C. famata

Themost common causes of nosocomial bloodstream infections are the *Candida* species[81]. *Candida famata* is a rare cause of invasive infection[82]. After its discovery in Japan, it was named as *Torula candida* and finally named *C. famata*[83]. It is found to colonizes skin, vagina, and oral cavity making it to be considered as a contaminant despite its isolation from clinical samples[83,84]. *C. famata* is an important opportunistic pathogen as it causes invasive candidiasis[84]. Intravenous catheter associated candidemia in immunocompromised patients has been reported to be caused by *C. famata* in a bone marrow transplant patient[85]. There have been reports of *C. famata* isolation in chronic intra ocular inflammation having endophthalmitis with, candidemia with aplastic anemia, and central catheterization likewise in a patient undergoing ambulatory peritoneal dialysis[86, (87), 88].

Table 2.1 Attributes of *Candida auris* a Menace in Public Health

Attributes	**Threats**
Increased prevalence, of unknown origin	Continuous increase in the future leads to emergence of *C. auris* as a frequent cause of nosocomial infections
Simultaneous emergence on *C. auris* infection	Worldwide dissemination leads to pandemics of different continents
Misidentification by diagnostic laboratories	Lack or delayed recognition of clinical cases leads to occult outbreaks
Biofilm formation, persistence/survival in the Environment	Inter-human transmission leads to nosocomial Outbreaks
Antifungal resistance (intrinsic or rapidly	Emergence of multidrug- or pan-drug–

inducible)	resistant strains lead to outbreaks with high mortality rate

Source: Borman, 2016

2.6 Antifungal Resistance Mechanisms in *C. auris* and other *Non-albicans Candida* (NAC)

Antifungal susceptibility testing of *Candida auris* and other (NAC) is recognized as a useful aid in optimizing the treatment of *Candida* infections as emergence of resistant strains continually threatens antifungal therapy. *C. auris* and other NAC have evolved to develop resistance to commonly used antifungal agents: azoles, echinocandins, polyenes, and nucleoside analogs thus making it responsible for its high rates of mortality around the globe. The intrinsic resistance is expressed by *C.auris* to all classes of antifungal drugs thus making this pathogen a menace in public health globally[89, 90]. In a study, it was discovered that *C.auris* isolates had resistance to fluconazole while it showed an elaborate MIC range to other antifungal drugs[91]. The Center for Disease Control provided tentative minimum inhibitory concentration breakpoints: 90 % of *C. auris* strains were resistant to fluconazole, 30 % to amphotericin B and 5 % to echinocandins[55].

Multidrug resistances were seen in 41 % of *C.auris* isolates and pan-resistance in 3–4 %[92, 93]. However, the CLSI and EUCAST susceptibility data on *C.auris* showed tentative minimum inhibitory concentration (MIC) breakpoints defining resistance as proposed: fluconazole, ≥32 µg/ml; voriconazole, ≥1 µg/ml; amphotericin B, ≥2 µg/ml; micafungin, ≥4 µg/ml and caspofungin, ≥2 µg/m[91, 94, 95]. The numerous antifungal resistance mechanisms exhibited by *C. auris* can be widely discussed as drug target mutation, drug purge or ejection, bio film formation and target overexpression[55]. The distinguished antifungal resistances shown in *C. auris* are not innate but of freshly gained trait, in which distinct clade variations in resistance are shown with coexistence of sensitive and resistant strains in the same population and varying resistance alleles on genetically related isolates[55, 96].

Two factors have proved to play a role in decreased susceptibility to antifungal treatments: molecular resistance mechanisms and biofilm-associated resistance mechanisms[97]. Genetic modifications in individual cells which decreases sensitivity to antifungals ultimately leads to resistance by any of the earlier mentioned ways: drug target modification, efflux pumpsover expression, or metabolism modifications and thus regarded as molecular resistance mechanism[98].

2.6.1 Mechanisms of Resistance to Azoles

Major Facilitator Superfamily (MFS) transporters and ATP Binding Cassette (ABC) efflux pumps overexpression.

Efflux pumps are proteins which transport components across the cell membrane, making them to pump drugs outside the cell thus lowering their concentration and sensitivity on the targeted cell. In Fig 2.1 (b), *C. auris* resistance in azoles by the way of multiple mechanisms: mutations and copy-number variations in *ERG11*and *TAC1B*, overexpression of Cdr1 and Mdr1 efflux pumps, and Hsp90-inducedazole tolerance[55]. The two major families of efflux pumps involved in antifungal resistance are ATP

Binding Cassette (ABC) and Major Facilitator Superfamily (MFS) transporters. The Enhanced overexpression of efflux pumps is one of the major resistance mechanisms to azoles in pathogenic *Candida* species[99].

Point mutations in ERG11

Ergosterol being a key membrane component in fungi, its biosynthesis is by the enzyme Lanosterol 14-alpha-demethylase (LD), encoded by the gene ERG11 which converts lanosterol to ergosterol. The LD is the primary target of azoles, which inhibits the function of the enzyme and ultimately stops ergosterol biosynthesis, thus impairing membrane integrity. Point mutations in ERG11 have been shown to reduce azole sensitivity in *Candida spp*., particularly in three "hot-spot" regions located between amino-acids 105–165, 266–287, and405–488[100].

ERG11 overexpression

The overexpression of ERG11 has been linked to a resistance to azole treatment, owing to increased production of LD which overwhelms the capacity of the antifungal to inhibit the activity of the protein, resulting in an active protein despite drugtreatment[101]. In *C. auris*, real time PCR experiments showed that in absence of fluconazole, there was no difference in ERG11 expression between fluconazole-susceptible and fluconazole-resistant strains[102].

2.6.2 Mechanisms of Resistance to Polyenes

There is little that is known regarding resistance of *C. auris* to polyenes, which includes the widely known amphotericin B, which acts by binding to ergosterol present in the fungal cell membrane which creates pores or holes in the membrane. In Fig 2.1 (a) Mechanisms include, non-synonymous mutations in *FLO8* and *utg4_968953* membrane transporter, Cdr6 and Opt1-likeefflux pumps, and *ERG1*, *ERG2*, *ERG6* and*ERG13* upregulation, thus killing the fungus by leaking its contents to the exterior[55]. Several *C. auris* strains have been resistant to Amphotericin B (AMB), themodifications in sterol composition of the membrane has proofed to be a resistance mechanism[103].

2.6.3 Mechanisms of Resistance to Flucytosine

Flucytosine being a nucleoside analog inhibits nucleic acid synthesis in the cell. The activation of flucytosine after entering the cell shows its antifungal action by requiring theprotein encoded by the gene FUR1[104]. In non-*aurisCandida* species mutations in FUR1 has been linked with flucytosine resistance[100]. A sequenced flucytosine resistant *C. auris* strain was observed to have F211I amino acid substitution in the FUR1 gene[105]. This specific missense mutation needs further studies to determine if this mutation is the cause of the resistance to flucytosine in the tested *C. auris* strain[106]. However, this drug is less employed than other antifungals, further research are to be done to understand the resistance of *C. auris* to this compound.

2.6.4 Mechanisms of Resistance to Echinocandins

The FKS1 and FKS2 genes encodes the Beta (1,3)D-glucan which is a key component of the fungal cellwall. When Beta (1,3)D-glucan synthase, an enzymeis inhibited by Echinocandins, there is decrease in the amount of glucans in the cellwall[34]. In Fig 2.1 (c) Resistance in echinocandin is by mutations in the *FKS1*genes, which reduce the affinity of β−1,3-glucansynthase for echinocandins[55]. *C.auris* strains that are echinocandin-resistant are known to be associated with substitution mutations of S639P, S639F and S639Yin their *FKS1* genes[55]. In figure 2.1 (d) below, biofilms resistance in *C. auris* is through the sequestering 50–90 % of the drug in the extracellular matrix, expressing large number of ATP-binding cassette (ABC) and the major facilitator superfamily (MFS) class of efflux pumps, and harbouringpersister cells, which can survive high levels of

environmental and chemical stress this happens in all forms of antifungal. (e) Increased levels of resistance in azoles are seen due to aggregative forms of *C. auris*.

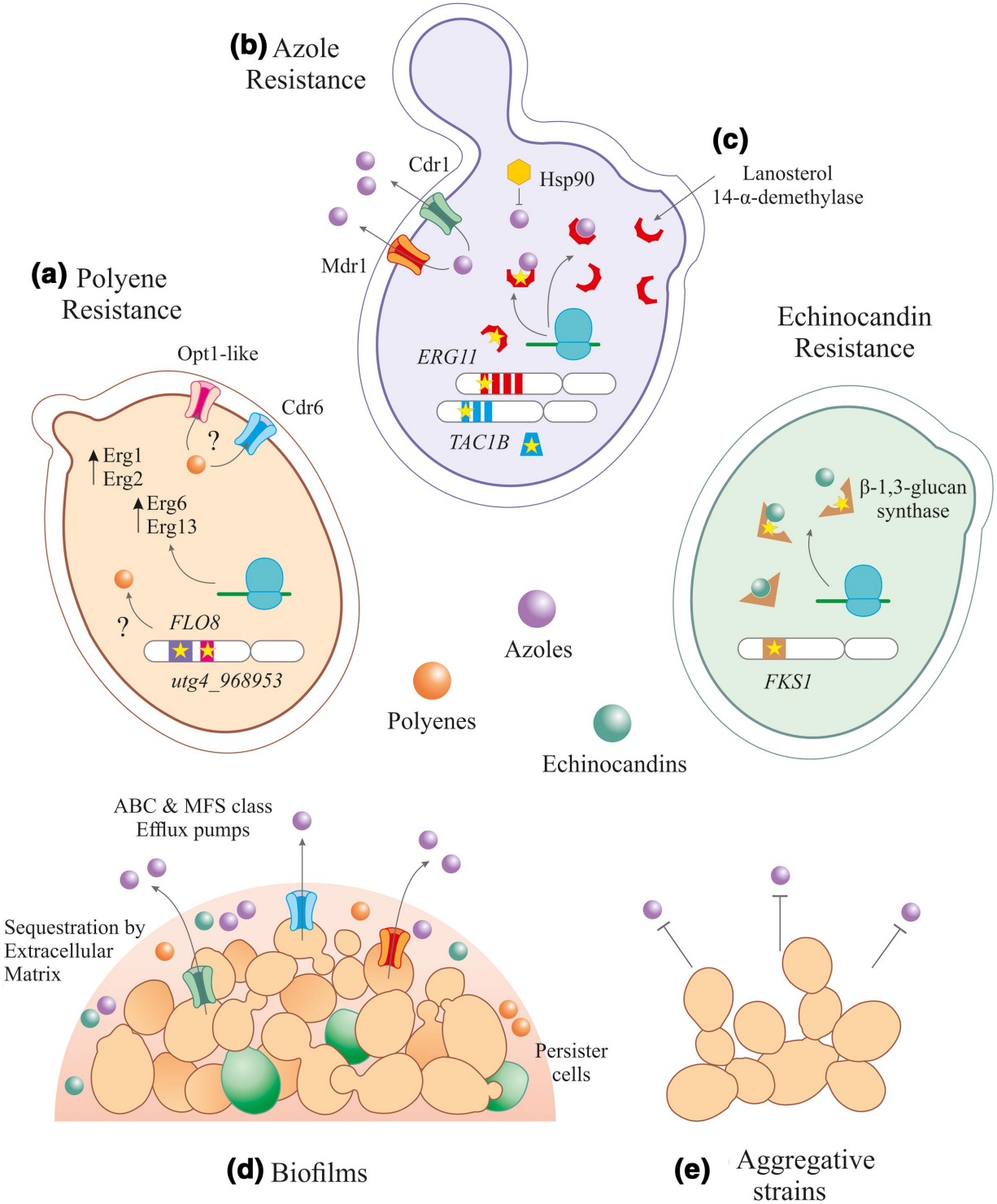

Figure 2.1 Antifungal resistance mechanisms in *C. auris*
Source: Chakrabarti and Sood, 2021

2.7 Pathogenesis and Virulence Factors of *C. auris*

The high mortality rate of infections associated with *C. auris* has been reported to be at many body areas like the skin, respiratory tract of humans, the urogenitals, these forms of infections can also spread rapidly into the bloodstream[39,90,107,108,]. To understanding the pathogenesis of *C. auris*infection from outset, the knowledge of its genome is essential[109]. *C. auris* possesses the required ability to cause infection in host; the virulence factors exhibited are similar in other pathogenic *Candida* species. These factors such as host cell adherence, germination, biofilm formation enhances its pathogenicity[26]. Many strains of *C. auris* are highly pathogenic when compared to *C. albican*[26,110]. These virulence factors are attributable to its ability to invade the host cells or evade immune system. The activities of proteinase and phospholipase have been demonstrated in *C. auris* and are known to be strain-dependent[111].

Table 2.2: *C. auris V*irulence Factors and Associated Resistance Genes

Virulence factors	Resistance genes
Hemolysin. Secreted Aspartyl proteinases. Secreted lipases Phosphatases. Mannosyl transferases Phospholipase Integrins. Adhesins. Zn (II) 2 cys 6 transcription factor (strain-specific degree of activity)	Azole's resistance Transportation of proteins and efflux pumps (ATP-binding cassette ABC; major facilitator superfamilies MFS; upregulation of CDR1, CDR2, MDR1) ERG 11 mutations (substitutions Y132F, K143R, and F126T) and ERG 11 upregulation Echinocandin resistance FKS1/2 (encoding echinocandin drug target 1,3-beta-glucan synthase) Adherence to surfaces and plastic materials (e.g., catheters) Biofilm formation Cellular morphology (aggregating and non-aggregating forms) Rudimentary pseudohyphae formation

Source: Borman, 2016

2.8 Infection Prevention and Control

In safe guiding the public health, infection prevention and control is paramount in cases of sporadic or outbreak of *C. auris* infection as this will curtail the menace the pathogen causes among infected patients thus leading to efficacy in drug treatment and decline in the high mortality rates associated with *C.auris*. That is why the CDC, ECDC and Public Health England have put up distinct recommendations and protocols in controlling any forms of outbreaks[14, 111,112]. In achieving this aim, several intermediacy ways, recommended actions and infection controls must be strictly followed. These includes the necessary actions of intervention, which involves the identification of *C. auris* cases including sporadic, the sites in which the pathogen was isolated both sterile and non-sterile, identification from previously known sites in the healthcare facilities or patients with international travels followed by screening of new patients with exposure to facilities with *C. auris* cases likewise from hospitals outside the country. The preliminary cultures from specimens associated with colonization of *C.auris*[111]. In all, there must be identification to the species level using PCR-sequencing of rDNA or any other culture independent identification method[113].

In respect to infection control, there should be contact with relevant health officials or research scientist for notification of an outbreak or sporadic case when identified to the spp level as this ascertains the presence of the pathogen, previously suspected cases a retrospective case finding should be embarked on and isolation of positive patients in individual rooms. In taking precautions, like hand washing hygiene with soap and water, then with alcohol-based sanitizer, wearing of personal protective equipment by

healthcare workers, environmental sanitation and patient decolonization. In decontamination of the skin using chlorhexidine, this can be achieved through body washes, mouth wash or gargling using chlorhexidine in patients with critical conditions in the intensive care unit on ventilators, use of chlorhexidine-infused pads in patients using catheter. *C. auris* is known for its multidrug resistant traits likewise affinity to spread rapidly in hospitals resulting in its high rates of mortality[114, 116- 118, 119-126]. In prevention of further spread of *C. auris* infection, infection control measures should be implemented even in the detection of sporadic cases as it will enhance epidemiological surveillance[126, 127, 92].

2.9 Treatment

Research has found out that there is more than 90% resistance to fluconazole, also that C. auris shows clade resistance with Clade I displaying a great level of it[34,128]. It has been known that clinical treatment in infections associated with *C. auris* is finite as a result of this; there is need for AFST as this will create a sort of surveillance[129].

There is need for a specialist in infectious diseases to be consulted, as recommended by CDC when intensive care is sort for patients infected with *C.auris*according to CDC guidelines, consultation with an infectious disease specialist ishighly suggested when caring for patients with *C. auris* infection[130]. The Infectious Disease Society ofAmerica (IDSA) suggests that for initial treatment of *C.auris* invasive infections, echinocandins be used as reduced susceptibility to fluconazole is high[131, 132]. In the course of treatment with echinocandin when seen that patient is susceptible to it and stable, fluconazole can be substituted after 5-7 days of treatment[132].

Nevertheless, mutations in FKS1 genes which causes resistance in echinocandins are common thus leading to failures in clinical treatment[102,133,134]. The susceptibility of amphotericin B serves as an alternative and voriconazole being a suitable drug of

choicein vitro susceptibility testing[135]. It has been known that only few treatment success rates has been made in the treatment of *C. auris* infection and this owes to the effect of antifungal low resistance rates[108]. In the advent of untreatable candidemia which is caused by *C. auris* isolates resistance to antifungal drugs[136]. In spite of treatments in invasive *C. auris* infections, patients are colonized for a long time[131].

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Chapter Three

Methodology

3.1 Research Design

This is a cross-sectional, hospital-based study.

Study site: Samples were collected from participants from three hospitals in Ibadan, Oyo State-Adeoyo Maternity Teaching Hospital (AMTH), Ring Road State Hospital (RRSH) and University College Hospital (UCH), Ibadan.

Study duration and sample collections: Clinical samples were from in and outpatients from various wards of the selected hospitals from between June and September, 2021. The participants were diagnosed of urinary tract infection, wound infection, otitis media, tuberculosis, genital tract infections, sinusitis, and vulvovaginitis.

Ethical Consideration: Approval was obtained from Ministry of Health, Oyo State: Research Ethics Committee, page 146.

Sample size: Using the prevalence of 50% (since there is no readily available data on the prevalence of *C. auris* in Nigeria). The formula for sample size determination indicated below was used: UNDP/World Bank (2001) on method of epidemiological research in communicable diseases:

$$N=\frac{Z^2P(1-P)}{D^2}$$

Where

N= Sample size

Z=Statistical reference confidence interval value at 95% =0.95

P=Estimated Prevalence of 50% i.e 0.5 (due to no data on prevalence of *C. auris* in Nigeria). The real prevalence and the epidemiology of *C. auris* still remain uncertain.

D = Highest acceptable error = 5%=0.05

Therefore,

$$N = \frac{0.95^2 x\ 0.5\ (1-0.5)}{0.05^2}$$

N = 90

Data Collection: Data on Socio-demographic information and Laboratory analysis were entered into Excel spread sheet.

Data analysis: Data were analysed using SPSS version.

3.2 Preparation and Sterilization of Media

Three media were used in this study: Sabouraud dextrose agar (SDA) (HiMedia, India), CHROMagar™ Candida Plus (CHROMagar™, France) and Tryptone Soy Broth (TSB). The Sabouraud dextrose agar (SDA) sterilized by autoclaving for 15 minutes at 121°C then supplemented with (0.5g/L) chloramphenical at 25-30°C as this will suppress the growth of bacteria. CHROMagar™ Candida Plus (CHROMagar™, France), a novel chromogenic medium for detection and differentiation of major clinical *Candida* species including *C. auris*. In preparing 100ml, 5.09g of the powder was weighed, heated and brought to boiling (100°C), cooled in a water bath to 45-50°C, stirred until the agar is well thickened and poured in a Petri dish using aseptical procedures. This preparation was done based on manufacturer's instructions. Tryptone Soy Broth (TSB) was sterilized by autoclaving for 15 minutes at 121°C. The TSB was used for storing the *C. auris* isolates.

3.3 Microbiological Analysis of the Specimen

Samples were processed following aseptical standard laboratory procedures for the isolation of *Candida* species using cultural methods[1].

3.3.1 Phenotypic Identification of *Candida auris* and other Non-*albican Candidas* on SDA and CHROMagar™ Candida Plus

The preliminary identification of *Candida* species from clinical samples after incubation at 37°C for 2 days produces smooth and white cream-colored colonies, followed by microscopic viewing of its wet preparations for identification of yeast cells. This was followed by Germ tube test, in which a small inoculum of the yeast cells from the SDA culture was suspended in 0.5 ml human serum, incubated at 37 °C for three hours and a drop observed on a microscope. Normal saline and a preparation of *C. albicans* ATCC 90028 was used as negative and positive controls respectively. *Candida* isolates with inability to form pseudohyphae which depicts negative germ tube test was subcultured on the Chromogenic medium. Identification of *Candida auris* was based on the phenotypic characteristics, colonial morphology and growth properties on CHROMagar™ Candida Plus which pale cream or fading purple to white colonies having a unique faint to strong blue tinge in the surrounding agar after 36 hours of incubation at 35°C (incubation conditions specified by the manufacturer).

3.4 Antifungal Susceptibility Testing

All isolates confirmed as *C. auris* from PCR amplification were subjected to AFST by testing for susceptibility to fluconazole[2,3].

Minimum Inhibitory Concentration (MIC)

Step1: Inoculation of overnight prepared TSB

Small colonies of confirmed *C.auris* isolates from PCR amplification were inoculated into 10 micro bottles containing overnight Tryptone Soya broth and inoculated at 37°C for 72 hours.

Step 2: Antifungal (Fluconazole) dilution to required concentration.

The dilution of the antifungal was carried out by diluting 100miligram of fluconazole powder in 10mls of sterile water (water for injection) thus giving 100,000 microgram/10mls of water for injection. The MIC of fluconazole against *Candida spp* is 16 microgram to 0.03 micrograms.

Step 3: Serial dilution of Fluconazole.

10 sterile tubes were arranged to give the concentrations of 16microgram to 0.03micrograms (µg) of Fluconazole MIC. 1ml of Tryptone soy broth was added into each of the tubes. 1ml of the 16microgram of fluconazole was added and mixed properly in the first tube followed by a serial dilution from the first sterile tube upto the 10^{th} sterile tube. 1ml was discarded from the last tube thus giving the following concentrations of fluconazole.

Tube 1	16 µg/ml
Tube 2	8 µg/ml
Tube 3	4 µg/ml
Tube 4	2 µg/ml
Tube 5	1 µg/ml
Tube 6	0.5 µg/ml
Tube 7	0.25 µg/ml
Tube 8	0.125 µg/ml
Tube 9	0.625 µg/ml
Tube 10	0.031 µg/ml

Step 4: This involves the subculturing each of the concentrations from the addition of 1 drop of the different concentrations of the antifungal in the overnight tryptone soy broth inoculated with the *C.auris* on SDA and incubation at 37°C for 72 hours. Visible

growths were seen from all the concentrations after 72 hours of incubation thus shown resistance to fluconazole.

3.5 PCR Procedures

3.5.1 DNA Extraction, Denaturation, Annealing and Extension

Freshly overnight grown *C. auris* colonies cultured from Tryptone Soy Broth (TSB) were picked using pipette tips and suspended in 200µl of isotonic buffer to a ZR BashingBead™ lysis tube followed by addition of 750µl BashingBead™ Buffer to the tube.

The ZR BashingBead™ lysis tube was centrifuged using a microcentrifuge at 10,000 revolutions per minute for 1 minute. The supernatant was transferred into a Zymo-Spin™ III-F filter in a collection tube and centrifuged at 8,000 revolutions per minute for 1 minute.

1,200µl of genomic lysis buffer was added to the filtrate in the collection tube; 800µl of it was transferred to a Zymo-spin™ IICR Column in a collection tube and centrifuged at 10,000 revolutions per minute for 1 minute.

The flow was discarded from the collection tube and centrifuged at 10,000 revolutions per minute for 1 minute.

DNA pre-wash buffer of 200µl was added to the Zymo-spin™ IICR Column in a new collection tube and centrifuged at 10,000 revolutions per minute for 1 minute.

DNA wash buffer of 500µl was added to the Zymo-spin™ IICR Columnand centrifuged at 10,000 revolutions per minute for 1 minute and transferred into a clean 1.5ml microcentrifuge tube to which 100µl DNA elution buffer was added directly to the column matrix andcentrifuged at 10,000 revolutions per minute for 30 seconds to elute the DNA as ultra pure DNA.

Standard PCR mix was prepared with Taq polymerase (EURx), with 1% DMSO added to enhance the reactions.

The PCR program consisted of 3 min denaturing at 94 °C, 30 cycles of 30 s at 94 °C, 30 s at 55 °C, and 20 s at 72 °C, followed by 3 min at 72 °C for final extension. After performing primer annealing optimization tests, PCR with *C. auris*-specific genes was executed with an annealing temperature of 55 °C.

3.5.2: Detection of PCR Products

PCR products were detected using agarose gel electrophoresis using 2% agarose gels. Bands of PCR products were captured using transilluminator.

Table 3.1: Target Genes and Primers used

Systemic ORF name	Primer name	Primer Sequence: 5′>3′	Amplicon size (bp)
QG37_03410	03410_F	GCCGCTAGATTGATCACCGT	137 (bp)
	03410_R	TAGGTGTGGGTACCCTTGGT	
QG37_05701	05701_F	GCAGCACTCGTGAGAGAACT	193(bp)
	05701_R	GGCTGGTTCTCCTGCTCATT	
	05701_F2	TGCAACCACAGTGACCAC	267(bp)
	05701_R2	CTTGCTACAGTCTGAGAG	
5.8s rDNA	RDN58_F	GGATCTCTTGGTTCTCGC	134(bp)
	RDN58_R	CGCTCAAACAGGCATGC	

Source: Ruiz-Gaitán, 2018

Chapter Four

Results and Discussion of Findings

4.1 Results and Findings

In this study, samples used were sputum, high vaginal and endocervical swabs, urine, ear swabs, and wound swabs with a total of 90 *Candida* species isolated from Adeoyo Maternity Teaching Hospital 42 (46.7%), Ring Road State Hospital 45 (50%) and University College Hospital 3 (3.3%) (Table 4.1) while overall distribution of samples in this study (Figure 4.1) were, high vaginal swabs n= 39 (43%), Pus/wound swab n=31 (34.4%), Ear swab n=11 (12%), Sputum, Endocervical swabs and Urine n=3 (3.3%) respectively. This report showed 38.9% (n=35) was confirmed *C.auris* using the Chromagar™ Candida Plus, from two hospitals out of three selected (Figure 4.2).

The distribution of *C.auris* in clinical samples among the hospitals in this study was represented in figure 4.3 with the highest in high vaginal swabs (n=8) followed by wound swabs (n=4) and ear swabs (n= 3) all from Adeoyo Maternity Teaching Hospital while in Ring Road State Hospital, wound swab accounted for the highest frequency (n=8) followed by high vaginal swab (n=7), ear swab (n=4) and sputum (n=1).

*C. auris*isolates were mostly isolated in females (*n* =24) and (*n* =11) from males (Table2). The result seen among the age groups, age groups 21-30 are 6 in Adeoyo Maternity Hospital and 10 from Ring Road State Hospital, 3 from Adeoyo Maternity

Teaching Hospital and 2 from Ring Road State Hospital were from 11-20 age groups, 4 Adeoyo Maternity Teaching Hospital and 3 from Ring Road State Hospital came from the age groups 31-40 and 2 from Adeoyo Maternity Teaching Hospital, 5 from Ring Road State Hospital age groups 41-50 (Figure 4.4). The phenotypic identification of *Candida auris*on CHROMagar™ Candida plus are shown in (Figures 4.5 and 4.6) white or pale cream to fading purple colonies having a unique faint to strong blue tinge in the surrounding agar, other *Candida* species (NAC) identified that are also emerging are: *C. krusei, C. famata, C. glabrata* and *C.tropicalis* were identified in this study (figures 4.7, 4.8, 4.9 and 4.10 respectively). The most isolated *Candida* species, *Candida albican* was also identified in this study, in figure 4.11.It is of interest seeing a wound swab that had a mixed growth of *C.tropicalis, C.famata and C.krusei* colonies (figure 4.12) on Chromagar™ Candida Plus. The figure 4.13, shows *Candida* species on both Chromagar™ Candida Plus and SDA.*Candida*spp distribution in this study using Chromagar Candida Plus is shown in (Figure 4.14) and the species distribution in each hospital using Chromagar™ Candida (Figure 4.15). The frequencies of co-morbidities found in this study are 5 in vulvovaginitis, 3 in chronic otitis media, 1 HIV and 2 sinusities (Figure 4.16). A high level of resistance to fluconazole was seen in all of the isolates of the isolates with minimum inhibitory concentration of 16µg/mL and 0.03µg/mL. There is need for further analysis on the genes responsible for the resistance. In the molecular analysis, 27 *C.auris* (Figure 4.20) was confirmed using the 5.8S rDNA having a 134(bp). Primers QG37_03410 and QG37_05701 (Figurer 4.17, 4.18, 4.19) did not show any corresponding band on the agarose gel electrophoresis.

Table 4.1: Frequencies of Samples from the Three Selected Hospitals

Sample Type	No. of samples from Adeoyo Maternity Teaching Hospital	No. of samples from Ring Road State Hospital	No. of samples from University College Hospital
Sputum	0	3	0
Ear swab	4	7	0
High vaginal swab	22	15	2
Endocervical swab	2	1	0
Pus/wound swab	12	18	1
Urine	*2*	1	0
Total	**42 (46%)**	**45 (50%)**	**3 (3.3%)**

Source: Laboratory analysis, 2022.

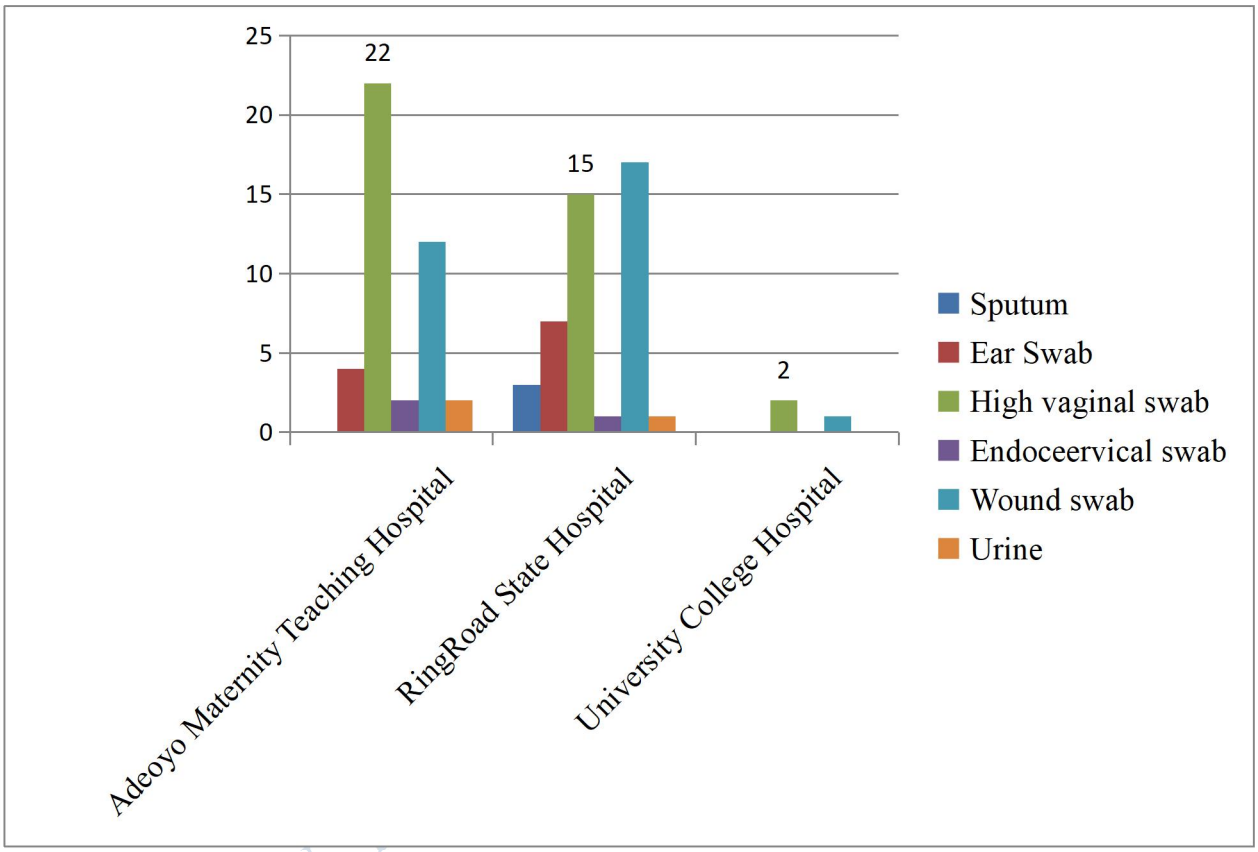


Figure 4.1: Overall Distribution of Samples in this Study
Source: Laboratory analysis, 2022.

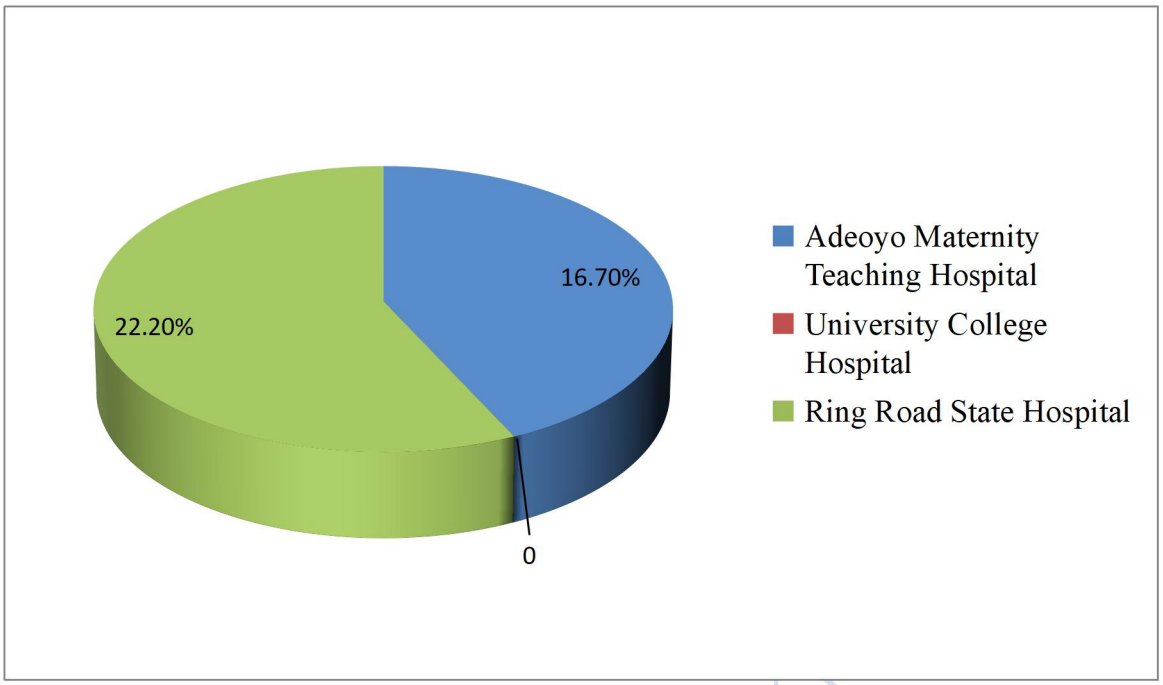


Figure 4.2: ***Candida auris*** **phenotypic distribution of Chromagar™ Candida Plus**
Source: Laboratory analysis, 2022.

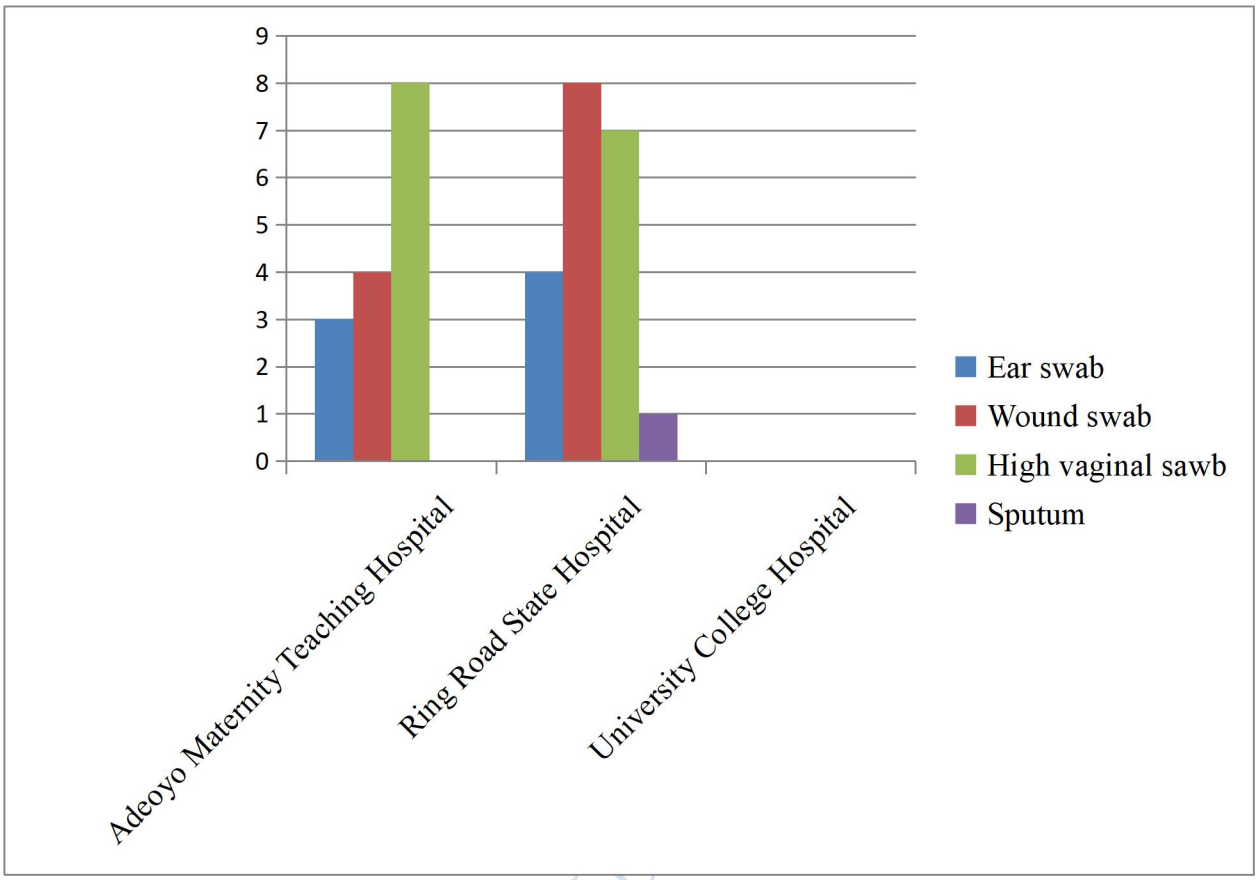


Figure 4.3: Distribution of *Candida auris* in clinical samples among hospitals in this study
Source: Laboratory analysis, 2022.

Table 4.2: Distribution of *C. auris* among gender

Sex	Adeoyo Maternity Teaching Hospital	Ring Road State Hospital	University College Hospital
Female	11 (31.4%)	13(37.1%)	NIL
Male	4 (11.4%)	7 (20%)	NIL

Source: Laboratory analysis, 2022.

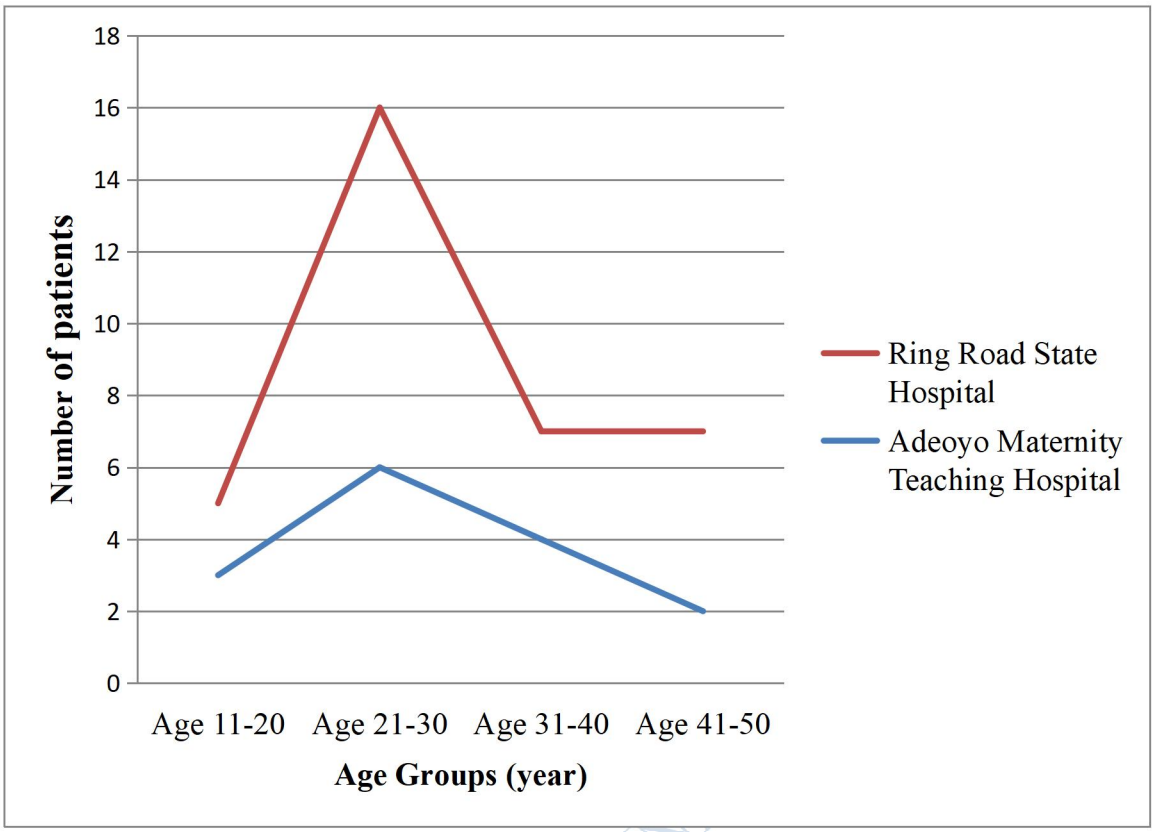


Figure 4.4: Age Distribution of Patients with *C.auris* in the Selected Hospitals
Source: Laboratory analysis, 2022.

Figure 4.5: *Candida auris* Differentiation on Chromagar^{TM}Candida plus amongSpecies.

Source: Laboratory analysis, 2022.

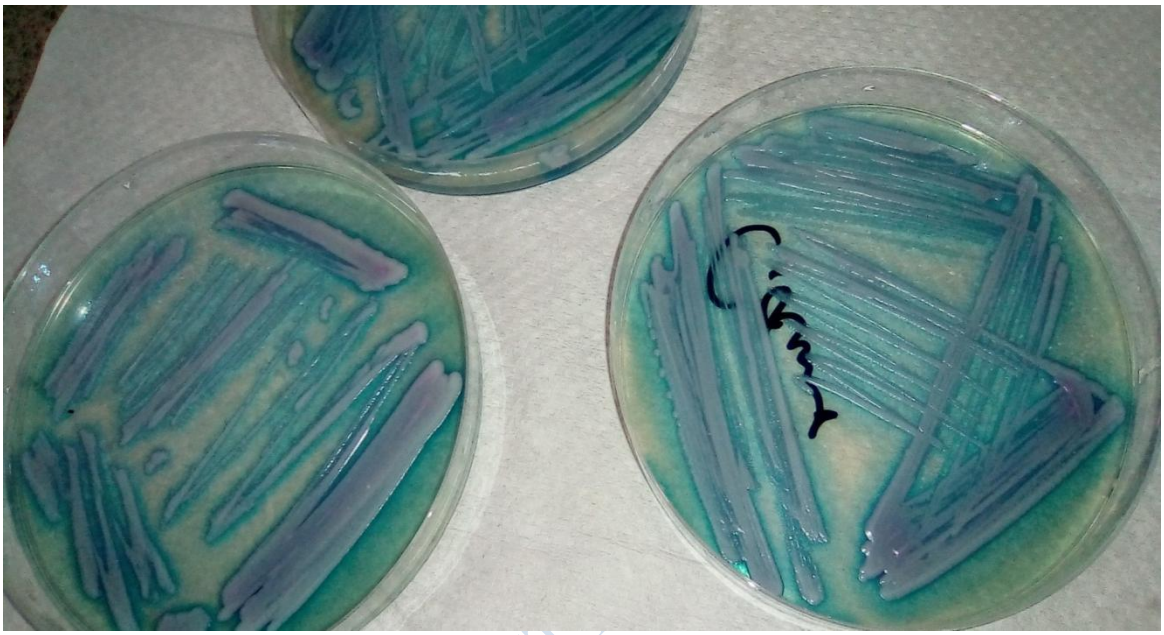


Figure 4.6: ***Candida auris***
Source: Laboratory analysis, 2022.

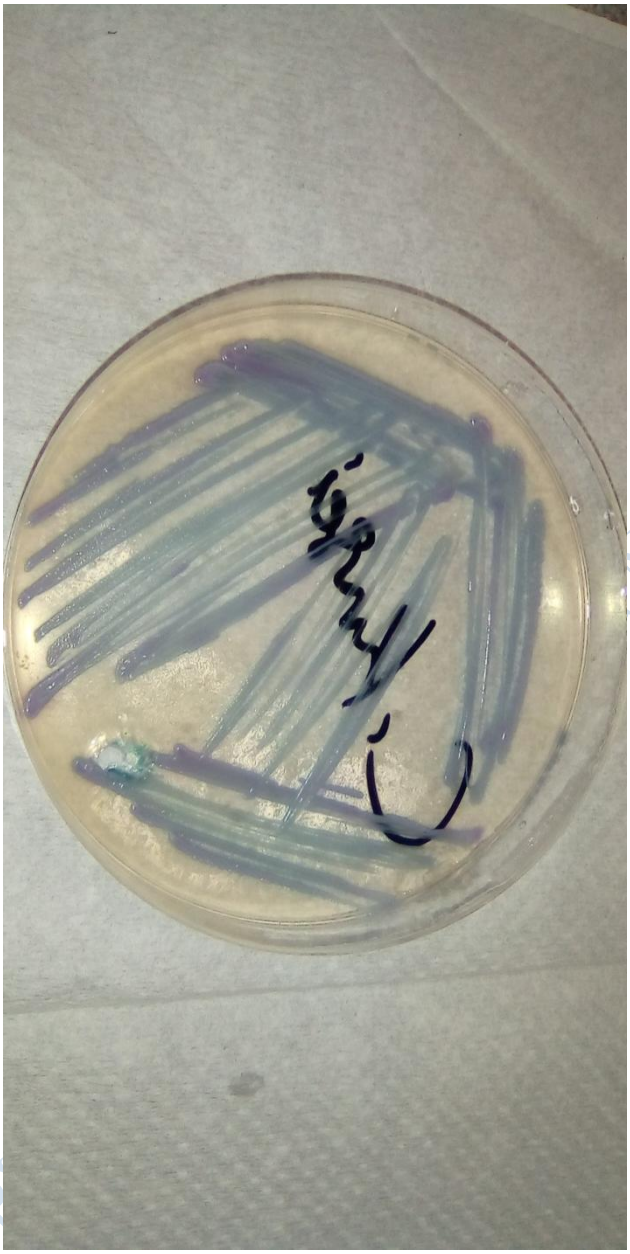


Figure 4.7: C*andida krusei*
Source: Laboratory analysis, 2022.

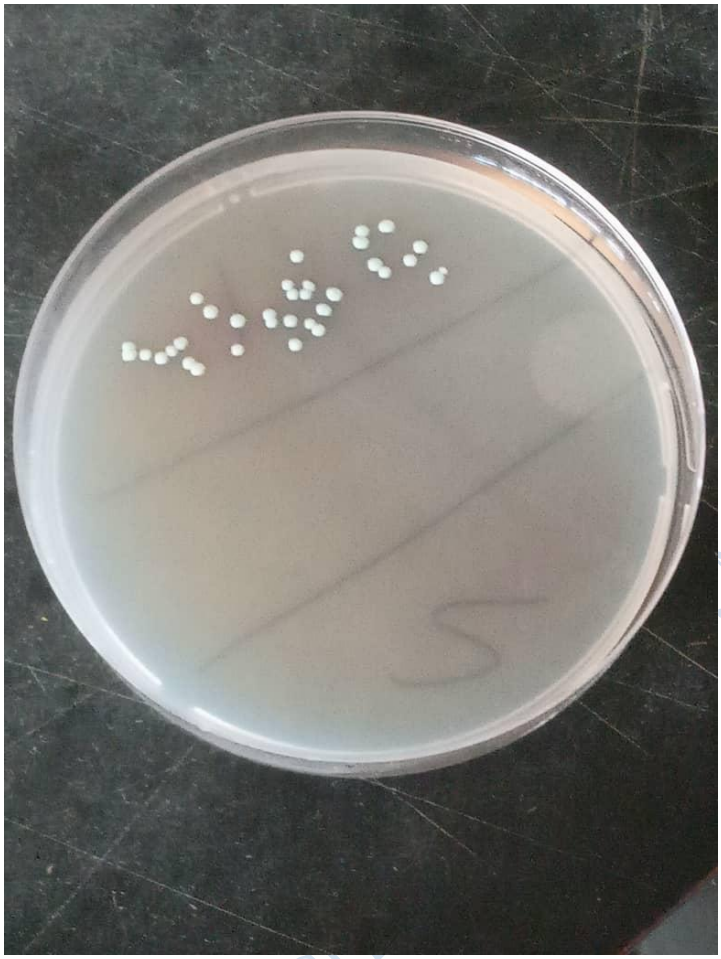


Figure 4.8: ***Candida famata***
Source: Laboratory analysis, 2022.

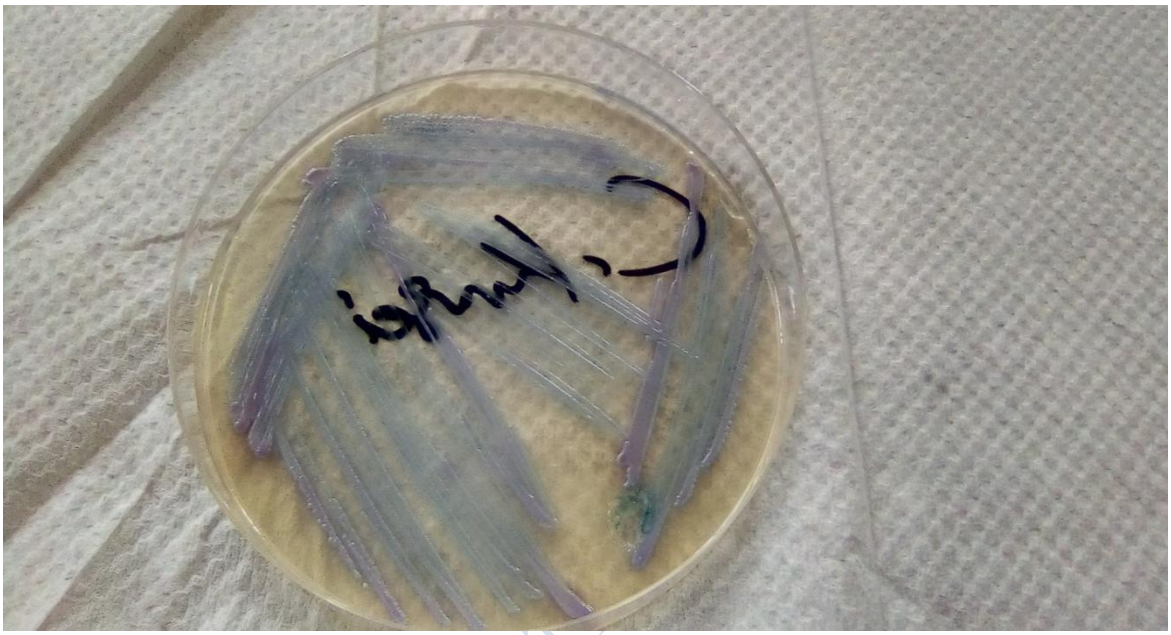


Figure 4.9: ***Candida glabrata***
Source: Laboratory analysis, 2022.

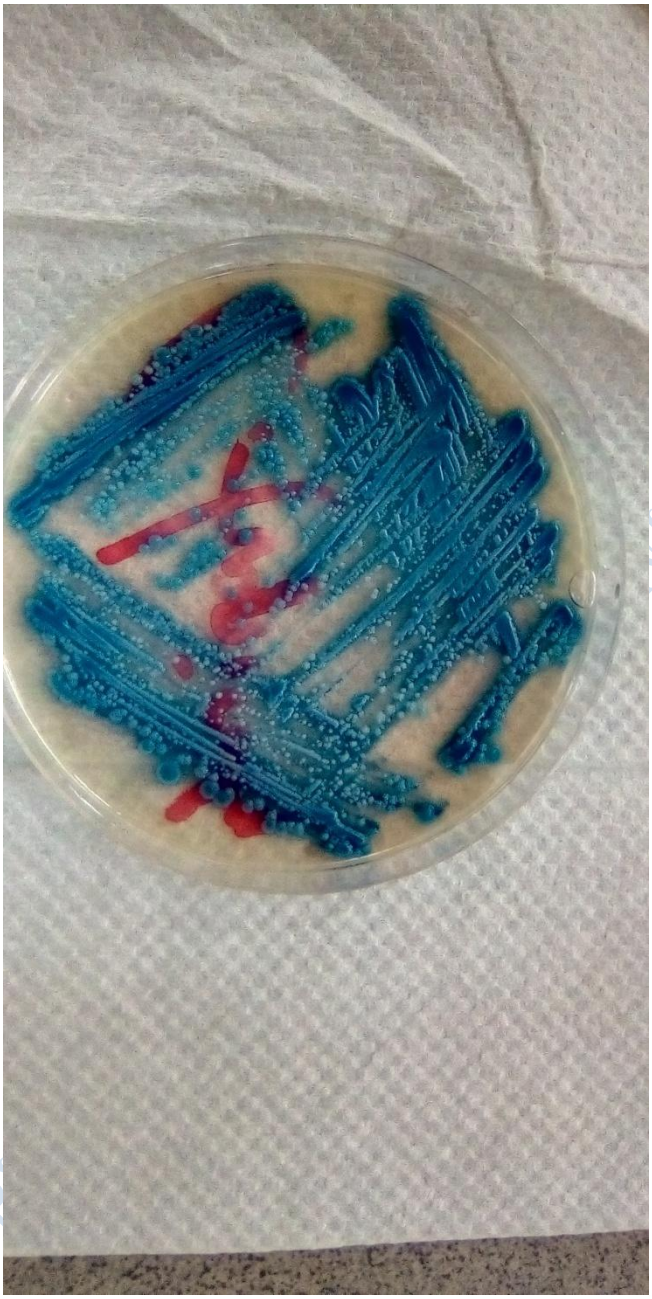


Figure 4.10: ***C.tropicalis***
Source: Laboratory analysis, 2022.

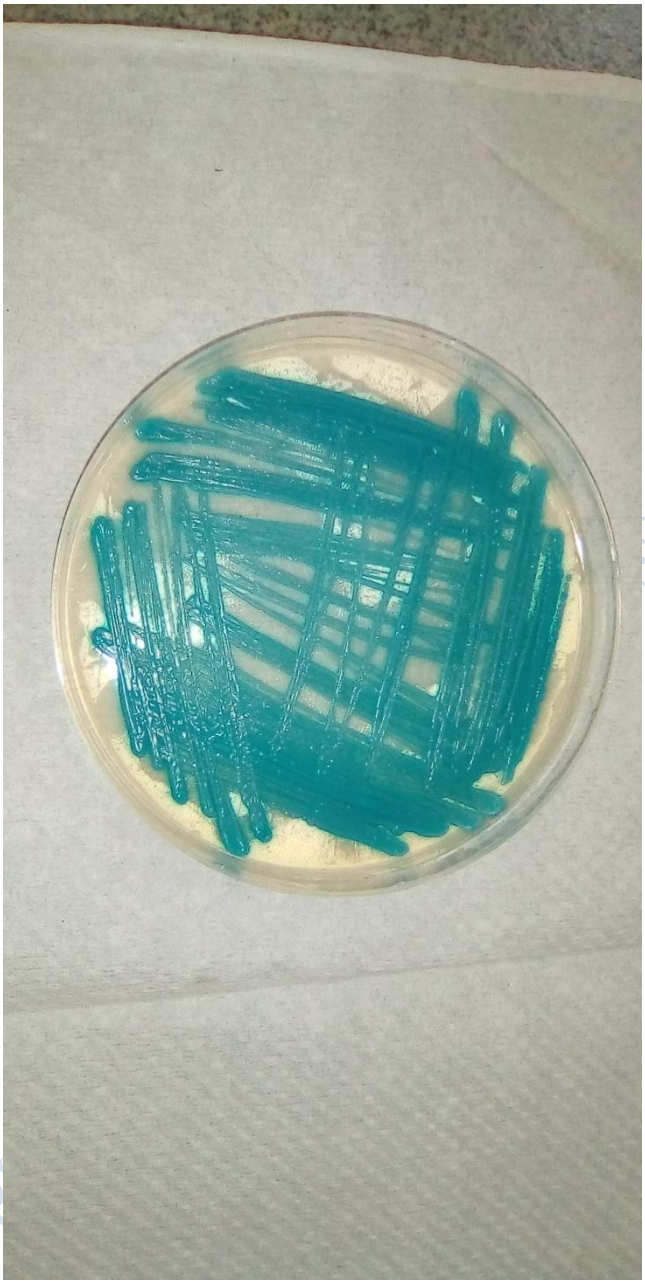


Figure 4.11: ***Candida albican***
Source: Laboratory analysis, 2022.

Figure 4.12: Mixed colonies of *C.tropicalis, C.famata and C.krusei*
Source: Laboratory analysis, 2022.

Figure 4.13: *Candida spp*on Chromagar™ Candida Plus and SDA
Source: Laboratory analysis, 2022.

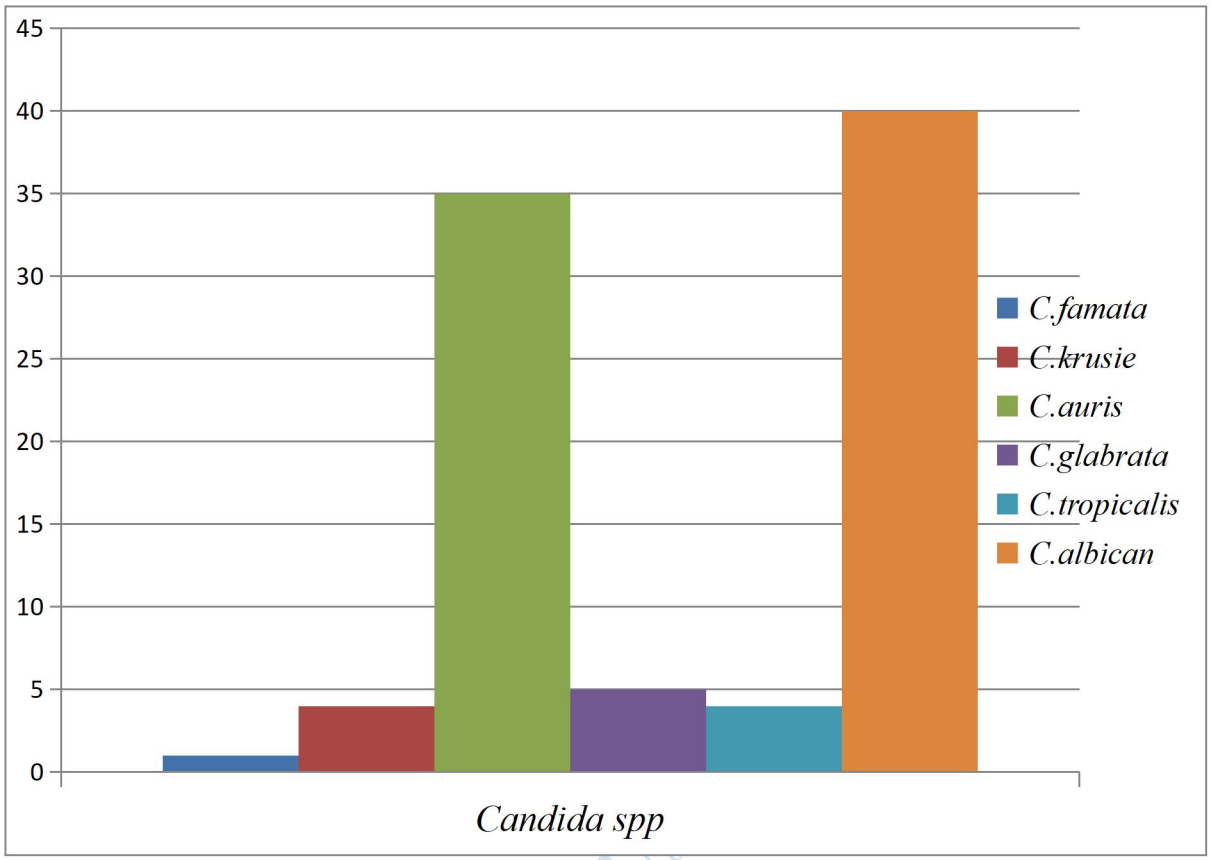


Figure 4.14: *Candida* species Distribution in this Study using Chromagar Candida Plus

Source: Laboratory analysis, 2022.

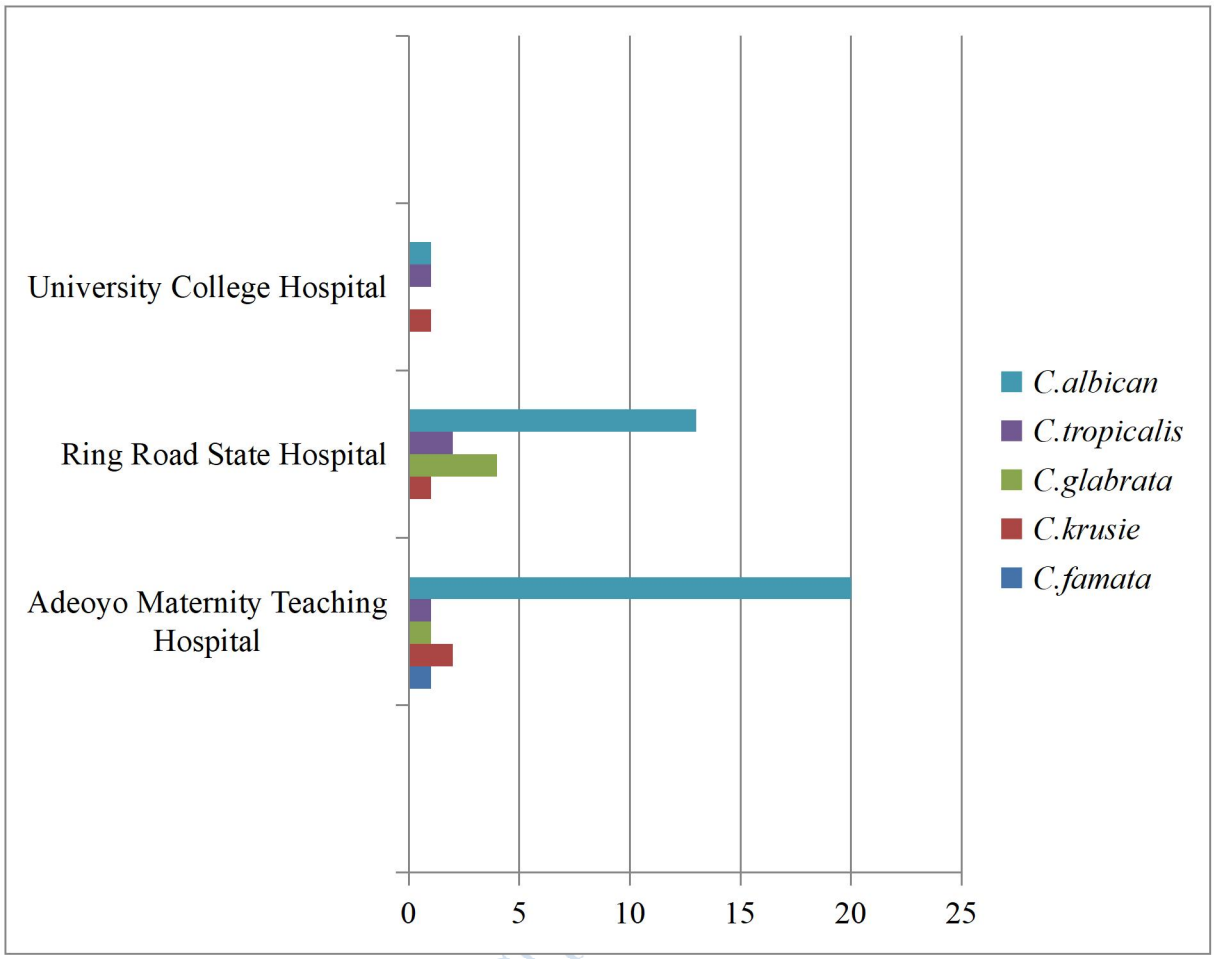


Figure 4.15: *Candida* species Distribution the Hospitals using Chromagar™ Candida Plus

Source: Laboratory analysis, 2022.

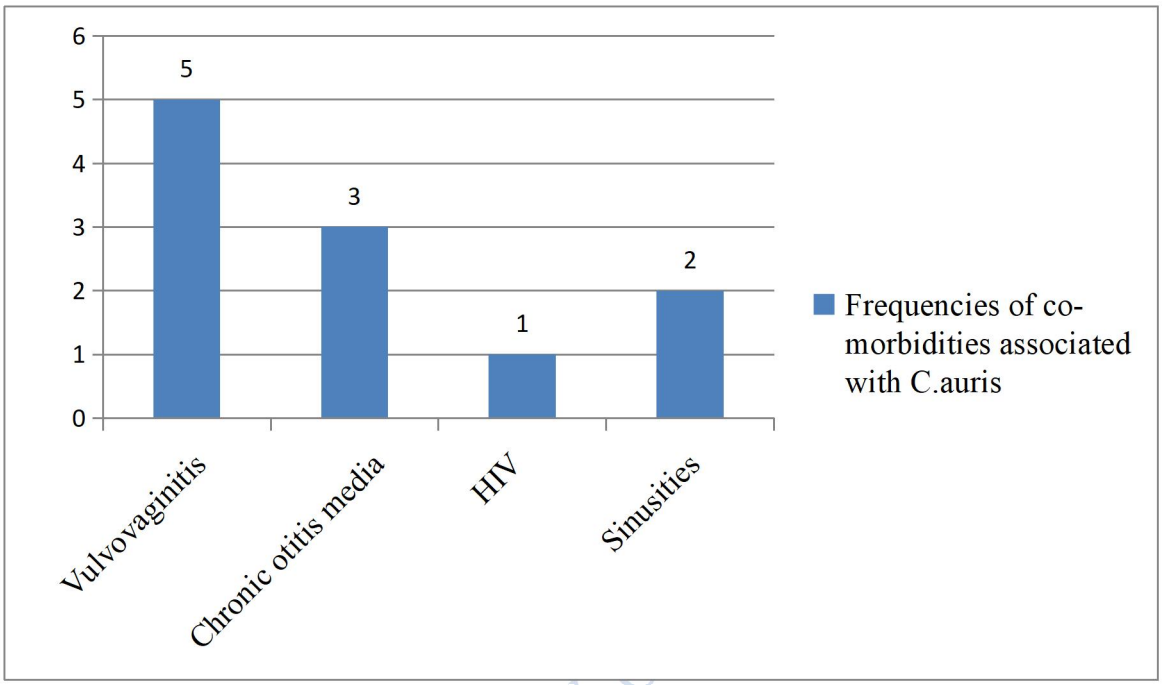
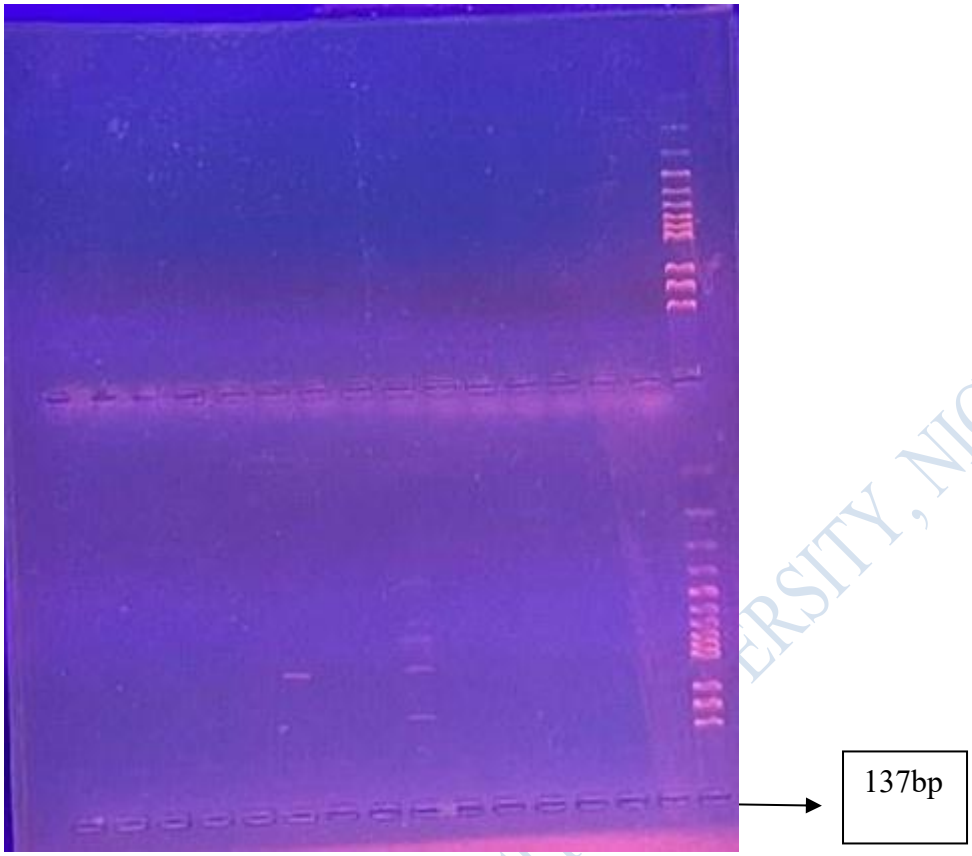


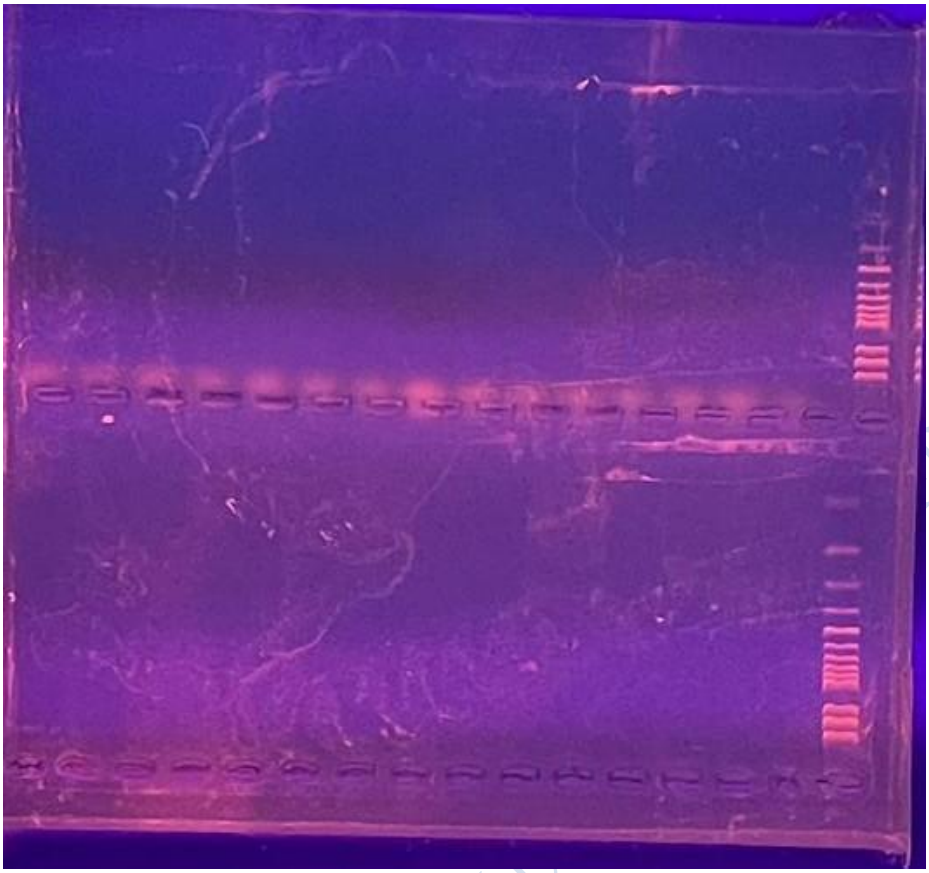
Figure 4.16: Frequencies of Co-morbidities associated with *C.auris*
Source: Laboratory analysis, 2022.



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 M

Figure 4.17: PCR for Detection of QG37_03410 Gene among C.auris isolates

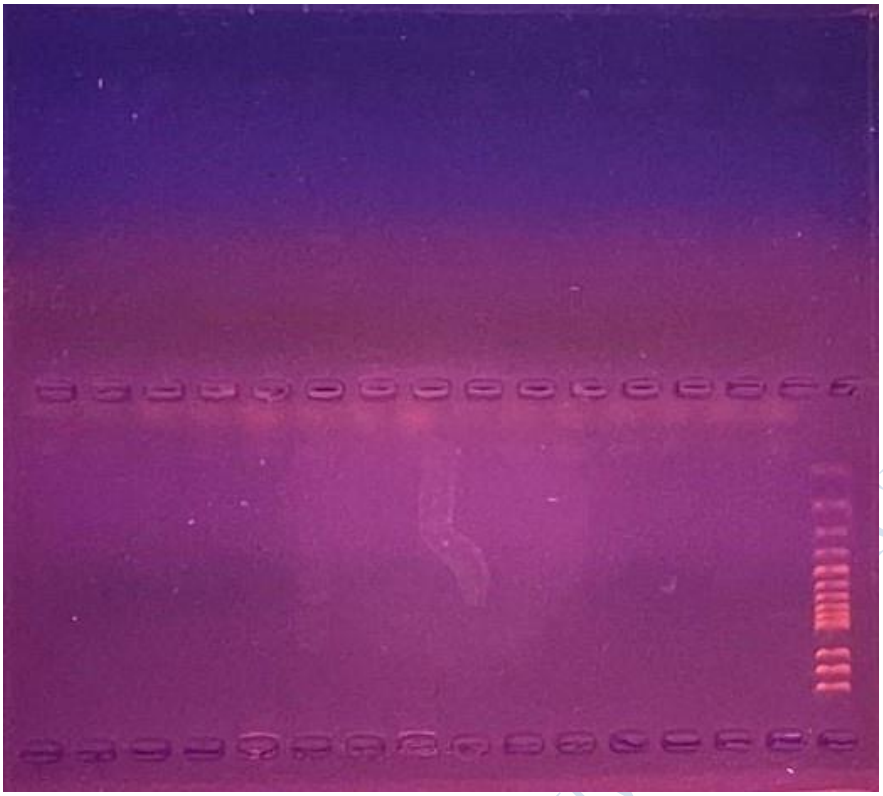
Source: Laboratory analysis, 2022.



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 M

Figure 4.18: PCR for Detection of QG37_05701 Gene among *C.auris* solates.

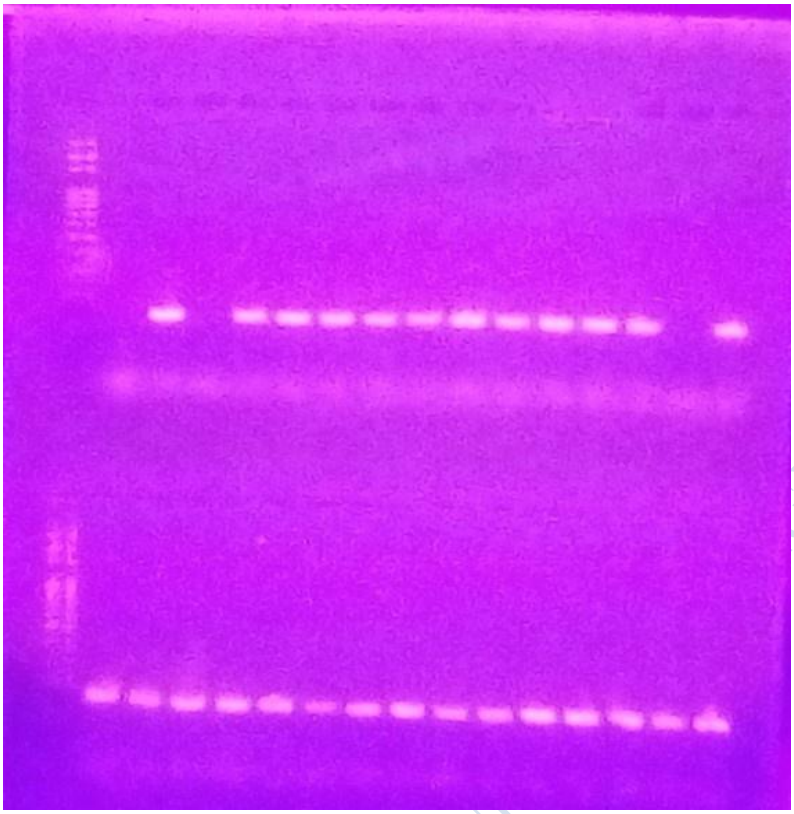
Source: Laboratory analysis, 2022.



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 M

Figure 4.19: PCR for Detection of QG37_05701 Gene among *C.auris* isolates.

Source: Laboratory analysis, 2022.



M 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
Figure 4.20: *C. auris* Detected from 5.8S rDNA Genes with 134bp
Source: Laboratory analysis, 2022.

4.2 Discussion of Findings

In this study, out of 90 *Candida* species isolated, crude sample frequencies from the three hospitals are: Adeoyo Maternity Teaching Hospital 42 (46.7%), Ring Road State Hospital 45 (50%) and University College Hospital 3 (3.3%) (Table 4.1) while overall sample distributions are, high vaginal swabs (43%), Pus/wound swab (34.4%), Ear swab (12%), Sputum, Endocervical swabs and Urine (3.3%) respectively (Figure 4.1). This report showed 38.9% (n=35) was confirmed *C. auris* using the Chromagar™ Candida Plus, from two hospitals out of three selected (figure 4.2). In corroboration of *C.auris* menance globally, Spain reported *C.auris* isolates n=42, in 2016, in 2013-2017 the United States of America reported n=232*C.auris* isolates, India reported n=243 in 2009-2015 which was far higher than number of isolates in this study[1, 2, 3, 4, 5, 6, 7]. This study ascertains the feasibility and provides valuable information to a further study in Nigeria. Low frequencies were reported in countries like South Africa from 2012 to 2015, Canada in 2017, Germany in 2015and Columbia in 2017 with number of *C.auris* isolates: 14, 5, 3 and 17 respectively[8, 9, 10, 11].

The distribution of *C.auris* in clinical samples among the hospitals in this study was represented in figure 4.3. The highest number was seen in high vaginal swabs (n=8) followed by wound swabs (n=4) and ear swabs (n= 3) all from Adeoyo Maternity Teaching Hospital while in Ring Road State Hospital, wound swab accounted for the highest frequency (n=8) followed by high vaginal swab (n=7), ear swab (n=4) and sputum (n=1). Comparing the totality of distribution in samples to other studies carried out, the total number of ear swabs is 7 in this study, is lower to the number of ear swabs from a study in South Korea[12]. The total number of wound swabs (n=12) and HVS (n=15) in this study is more than high vaginal swab n=1 and wound swab n=3 reported in India and United Kingdomrespectively[13,14,15].

Table 4.2 shows the distribution of *C. auris* among gender.It was seen that the females from RRST had the highest occurrence of *C. auris* 13(37.1%), followed by 11% occurrence seen in AMTH while in UCH, it was absent in the females. In total of this study, as related to other study had isolates mostly isolated from females (*n* =24) and (*n* =11) from males likewise in South Africa (female7 and male3) but in United Kingdom, there were more males n=33 than females n=17 which is similar to India with male n=108 and females n=37[9, 16, 17]. There is yet to be any link provided for the gender differences in *C.auris*infections[18]. In this study, the age group with the highest incidence of *C.auris* is age group 21-30; the lowest is age group 11-20 while the age groups 31-40 and 41-50 had the same value (Figure 4.4). The pattern of differences in gender likewise age group maybe peculiar to race globally, individual way of living or the state of healthcare facilities as it plays its crucial part.

The phenotypic identification of *Candida auris* on CHROMagar™ Candida plus in this study gave pale cream or fading purple to white colonies having a unique faint to strong blue tinge in the surrounding agar (figures 4.5 and 4.6) which differentiates it from other *Candida* species, after 36 hours of incubation at 35°C this was also observed in a study carried out on strains from isolates identified at the UK National Mycology Reference Laboratory (MRL)[19]. The use of this novel chromogenic medium, has identified other emerging *Candida* species: *C.krusei, C.famata, C.glabrata* and *C.tropicalis* were identified in this study (figures 4.7, 4.8, 4.9 and 4.10) respectively. The most isolated *Candida albican* was also identified in this study (figure 4.11). It is of interest seeing a wound swab that had a mixed growth of *C.tropicalis, C.famata and C.krusei* colonies (figure 4.12) on Chromagar™ Candida Plus. The figure 4.13 shows *Candida* species on both Chromagar™ Candida Plus and SDA.*Candida* spp distribution in this study using Chromagar Candida Plus is shown in (figure 4.14).

The frequencies of other *Candida* species isolated in Adeoyo Maternity Teaching hospital were: *C.famata* n=1, *C.krusie* n=2, *C.glabrata* n=1, *C.tropicalis* n=1, *C.albican* n=20 while in Ring Road State Hospital, *C.famata* n=1, *C.krusie* n=4, *C.glabrata* n=2, *C.tropicalis* n=2, *C.albican* n=13. In UCH, *C.albican* n=1, *C.krusie* n=1 and *C.tropicalis* n=1(figure 4.15).

Majority of patients having infections or diseases have one or more underlying health conditions and *C. auris* infectionis not an exception of it. Co-morbidities associated with *C.auris* as reported in this study (figure 4.16), shows vulvovaginitis 14.2% with the highest frequency followed by chronic otitis media 8.6%, sinusities 6%, and HIV had 2.8% frequency when compared to a study in which diabetes had the highest frequency in Venezuela (2012-2015) while vulvovaginitis, sinusities and HIV were lowest frequencies in Isreal (2014-2015), Japan(2009) and Venezuela (2012-2015) respectively[20, 21,9].

A high level of resistance to fluconazole was seen in all of the isolates of the isolates with minimum inhibitory concentration of 16µg/mL and 0.03µg/mL. There is need for further analysis on the genes responsible for the resistance.

This PCR method is based on amplifying fragments of species-specific GPI protein-encoding genes which is different from ITS2 sequence PCR identification, but it is simple, fast also accurate which identifies *C.auris* in clinical samples. It is very important to get right the diagnosis in cases of *Candida* infections up to the species level. The accuracy and rapidness in diagnosis of *C.auris* is of utmost importance in combating the menace, success of drug therapy and the control of this emerging pathogen[22,23].

In the molecular analysis, 27 *C. auris* (Figure 4.20) was confirmed using the 5.8S rDNA having a 134 (bp). In PCR amplification of QG37_03410 and QG37_05701 fragments to identify *C. auris*, (Figures 4.17 and 4.19) did not show any corresponding band on the agarose gel electrophoresis likewise on figure 4.18 whereas PCR amplification of QG37_03410 and QG37_05701 fragments to recognize *C. auris* yielded a positive result in a research conducted[1]. The *C. auris* isolates analyzed in this study were from Ibadan, Oyo state and none of the patients had any international travel history, this indicates that by further analysis of WGS, there is a potential West African Clade to be added to the existing clades.

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Chapter Five

Conclusion

5.1 Summary of Findings

The emerging *Candida* specie, *Candida auris* and other non-*albican Candida* (NAC) were isolated in this study using the novel Chromagar™ Candida Plus, a chromogenic medium: cultured from patient specimens from the study area. *Candida albicans* was the most prevalent followed by *Candida auris,* others isolated were *Candida krusei, Candida glabrata, C.famata, C.tropicalis* owing to their repectives color colonies of purple, pink, white and deep blue on the novel Chromagar™ Candida Plus. A high level of resistance to fluconazole was seen in all of the isolates of the isolates with minimum inhibitory concentration of 16µg/mL and 0.03µg/mL. Co-morbidities associated with *C.auris* found in this study shows vulvovaginitis having the highest frequency of 14.2%, followed by chronic otitis media with 8.6%, and HIV with the lowest frequency at 2.8%. It is of interest that a mixed growth of (NAC) non-*albican Candida*from a sample of wound swab had *C.tropicalis, C.famata and C.krusei* colonies on Chromagar™ Candida Plus. The PCR method used in this study amplifies fragments of species-specific GPI protein-encoding genes thus confirms the identification to species level of *C. auris* from the novel Chromagar™ Candida Plus used in the cultural method.

5.2 Conclusion

This research work confirms the presence of the emerging *Candida auris* likewise other non-*albican Candida* (NAC) from two hospitals out of the three hospitals where the study was conducted. The use of rapid diagnostic methods in fungal infections must be of priority inorder to curtail the menance fungal infections causes globally. In cases of candidaemia, *Candida auris* has emerged to be a significant pathogen in healthcare facilities which its transmission is on the increase throughits ability to adhere to the skin, non-sterile body sites, abiotic surfaces and the invasion of the blood stream. The use of chromogenic agar in this study made it possible to phenotypically detect *Candida auris* with its distinct colour and which is evident of the presence of this emerging multi-drug pathogenic *Candida* specie in Nigeria and particularly in Oyo state. The infection prevention and control to safe guiding the public health, is paramount in cases of sporadic or outbreak of *C. auris* infection as this will curtail the menace the pathogen causes among infected patients thus leading to efficacy in drug treatment and decline in the high mortality rates associated with *C.auris*.

5.3 Recommendations

1. It is recommended that routine detection and characterization of *candida auris* and other non-*albican Candida* (NAC) should be intergrated into routine procedures in medical microbiology laboratories to prevent missing out these pathogens from clinical samples.
2. Routine determination of antifungal susceptibility testing of *candida auris* and NAC isolates from clinical sample is recommended to prevent in appropriate use of antifungal drugs.
3. Further studies into *C.auris* specific clades, as there is a potential discovery of West African clade using Whole Genome Sequencing to point out the genetic/genomic differences in different *C. auris* strains from different locations.
4. There should be infection prevention controls measures readily put in place and constantly carried out in all healthcare facilities in Nigeria as this will prevent the spread or transmission of the multi-drug resistant *Candida auris.*
5. The field of medical mycology in microbiology should be given priority like it is being given to the fields of virology and bacteriology in microbiology at finding preventive measures, disease survalliance and other healthcare policies against sporadic or outbreaks of infectious diseases.

5.4 Contribution to Knowledge

This research contributes to knowledge as it creates the awareness in the public health sector and medical diagnostic laboratories that the emergence of *Candida auris* and other non-*albicanCandida* in Nigeria was confirmed and that medical diagnostic laboratories should identify any *Candida spp* down to the species level as this will enhance effective clinical treatment theraphy thus curbing the menance these emerging multidrug resistant non-*albican Candida* causes in the health sector. The usage of chromogenic agar like CHROMagar^{TM} Candida Plus has greatly helped and improved the phenotypic detection, identification and differentiation of major clinical *Candida* species, including *Candida auris* from the most prevalent *Candida albican* all over the globe also in this conducted research. This conducted research elucidates on the the molecular technology, PCR method used in the identification of the phenotypically identified *Candida auris* is based on amplifying fragments of species-specific GPI protein-encoding genes which is different from ITS2 sequence PCR identification technique, is simple, fast and accuratly identifies *C. auris* in clinical samples as it is very important to get right the diagnosis in cases of *Candida* infections up to the species level.

5.5 Suggestions for Further Research

Whole genome sequencing is suggested to be used for further studies inorder to group the *C.auris* strains found in this study into clades based on differences in number of single-nucleotide polymorphisms (SNPs) into existing clades or potential sixth clade, West African clade. There should be further studies carried out on the pathogen using other molecular techniques to identify *C. auris* to the species level in other geopolitical zones in Nigeria as this will give more data on the prevalence of this organism.

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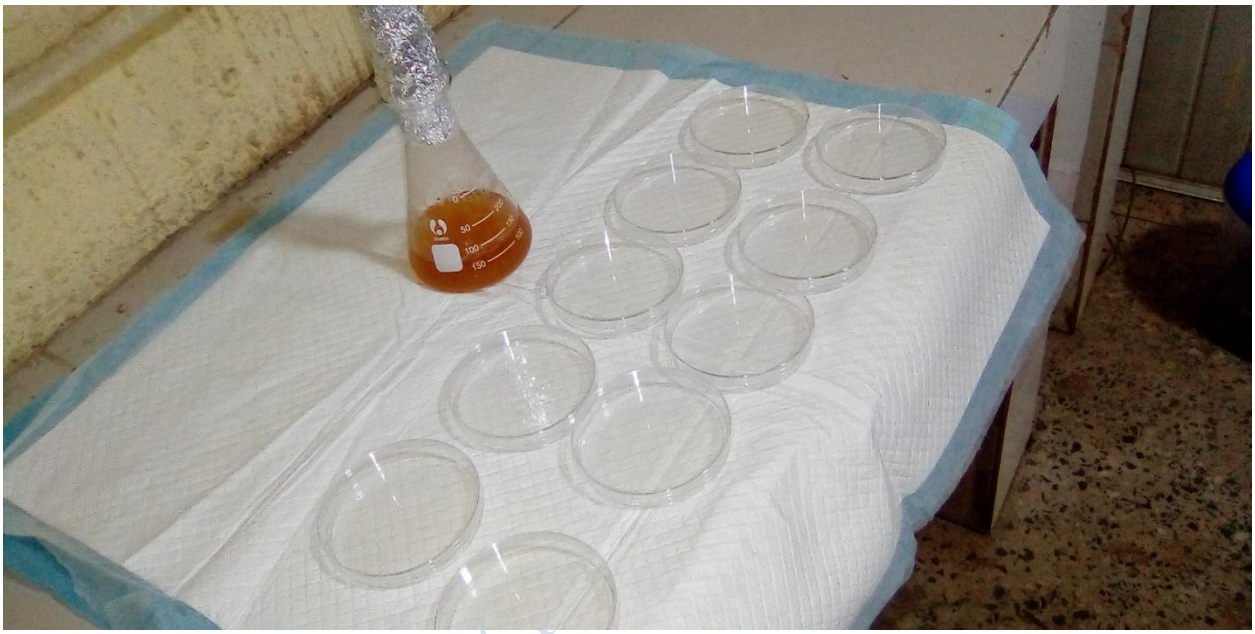
Appendix I

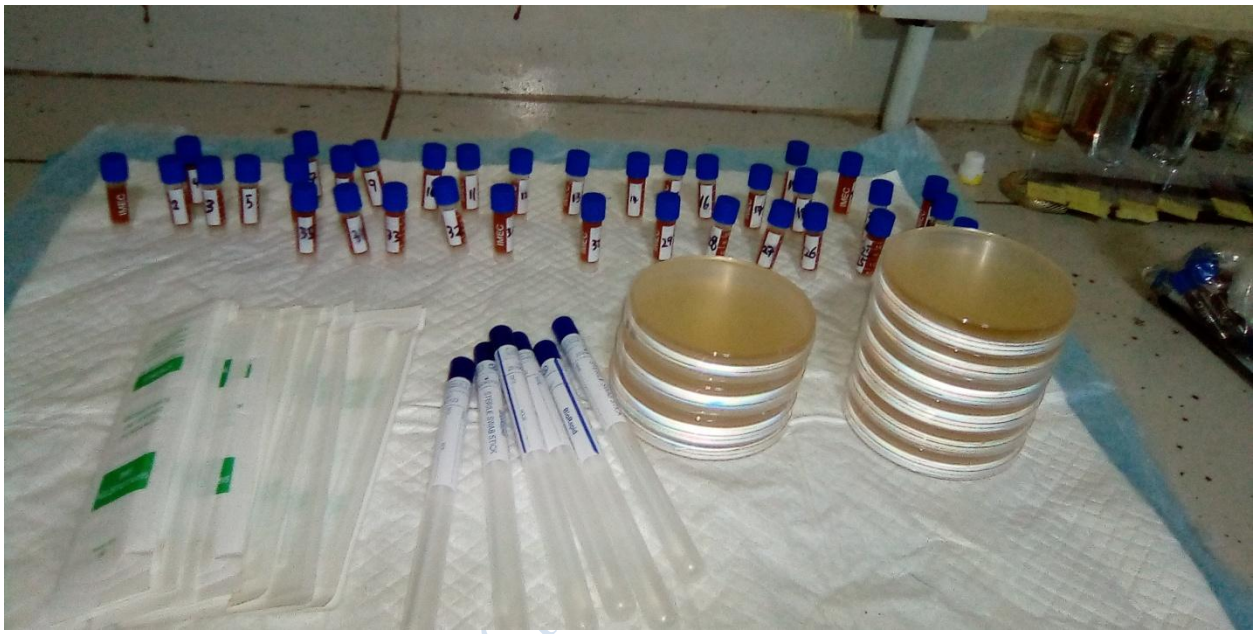


Sterilized Chromagar™ Candida Plus

Appendix II

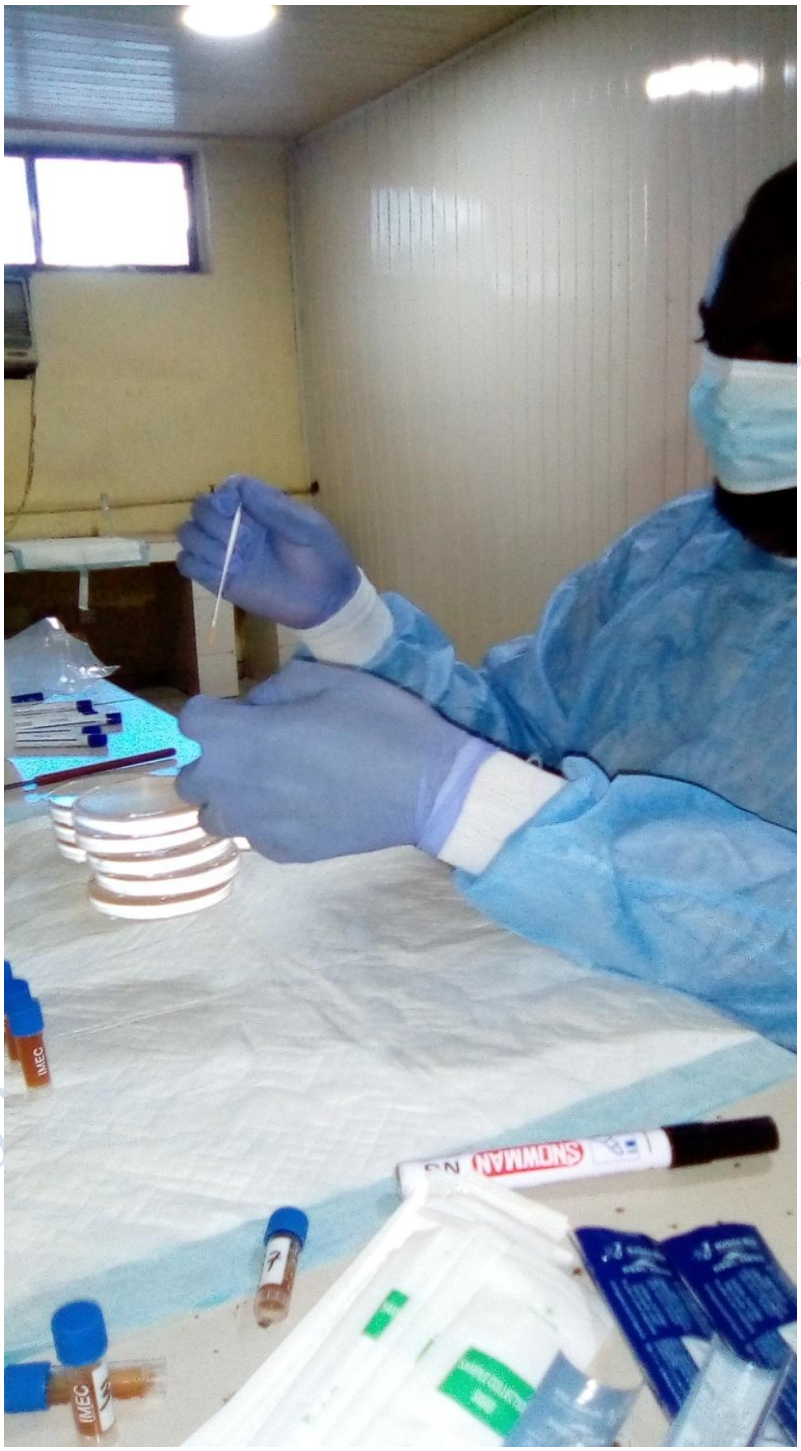
Aseptically pouring of the Sterilized Chromagar™ Candida Plus

Appendix III



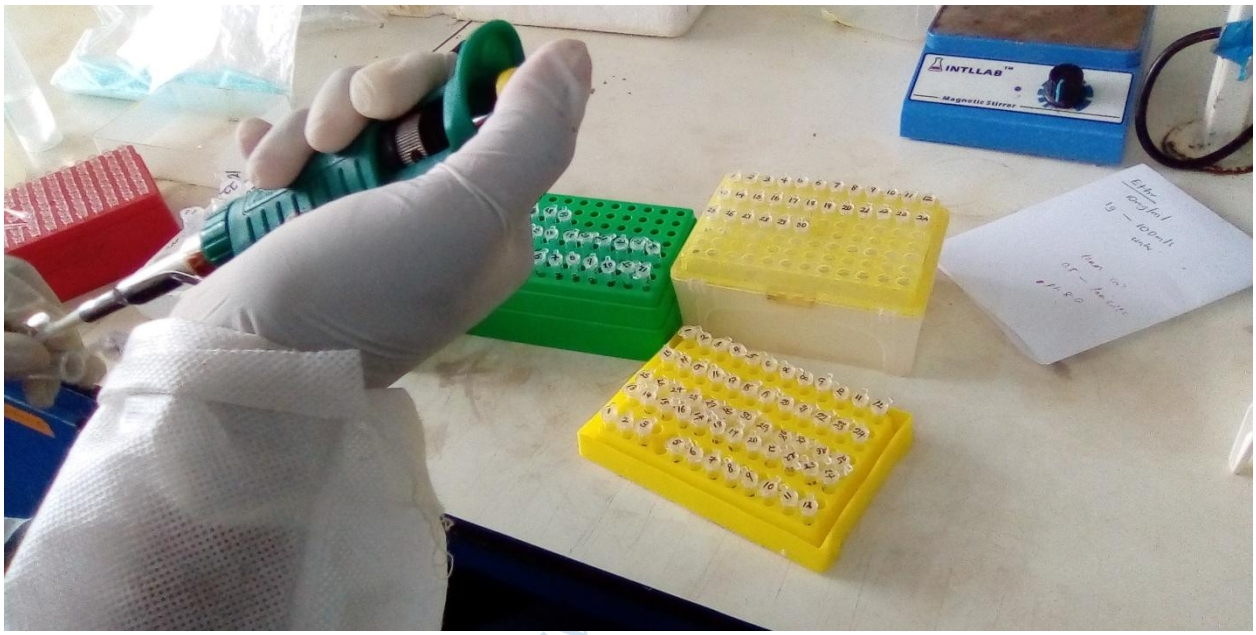
C.auris **isolates in TSB to be subcultured on Chromagar™ Candida plus using sterile swab sticks.**

Appendix IV



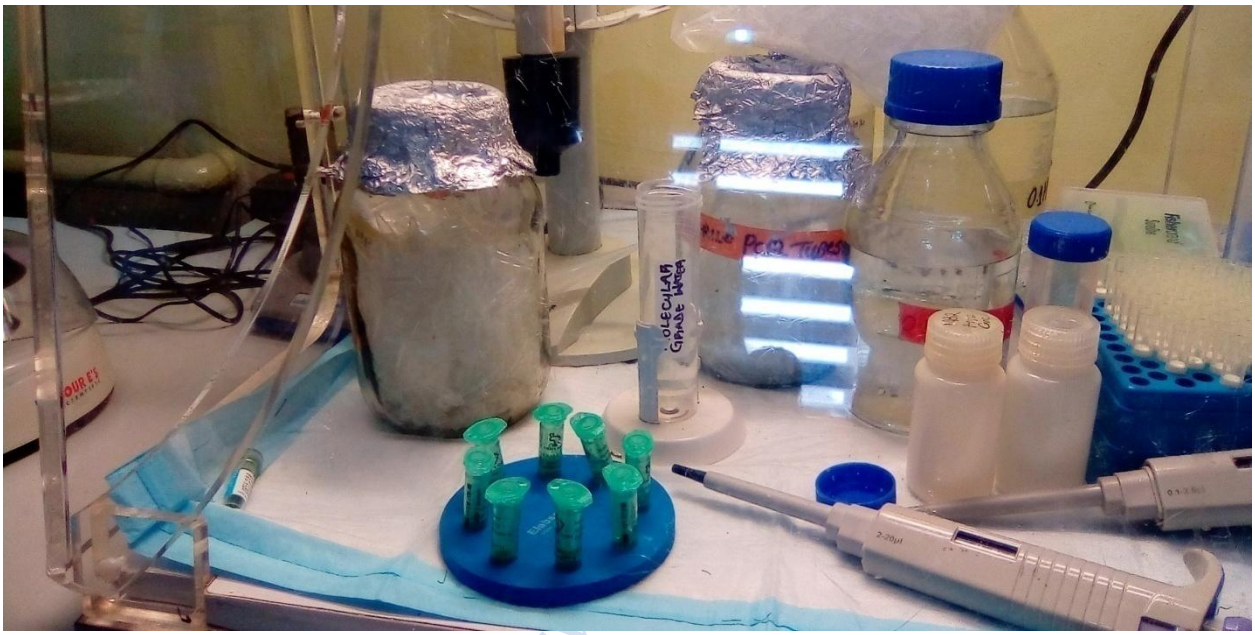
Culturing the C.auris isolates on Chromagar™ Candida Plus

Appendix V



Extracted *C.auris* DNA in PCR tubes.

Appendix VI



Constituted *C.auris* primers under Ultra violet light

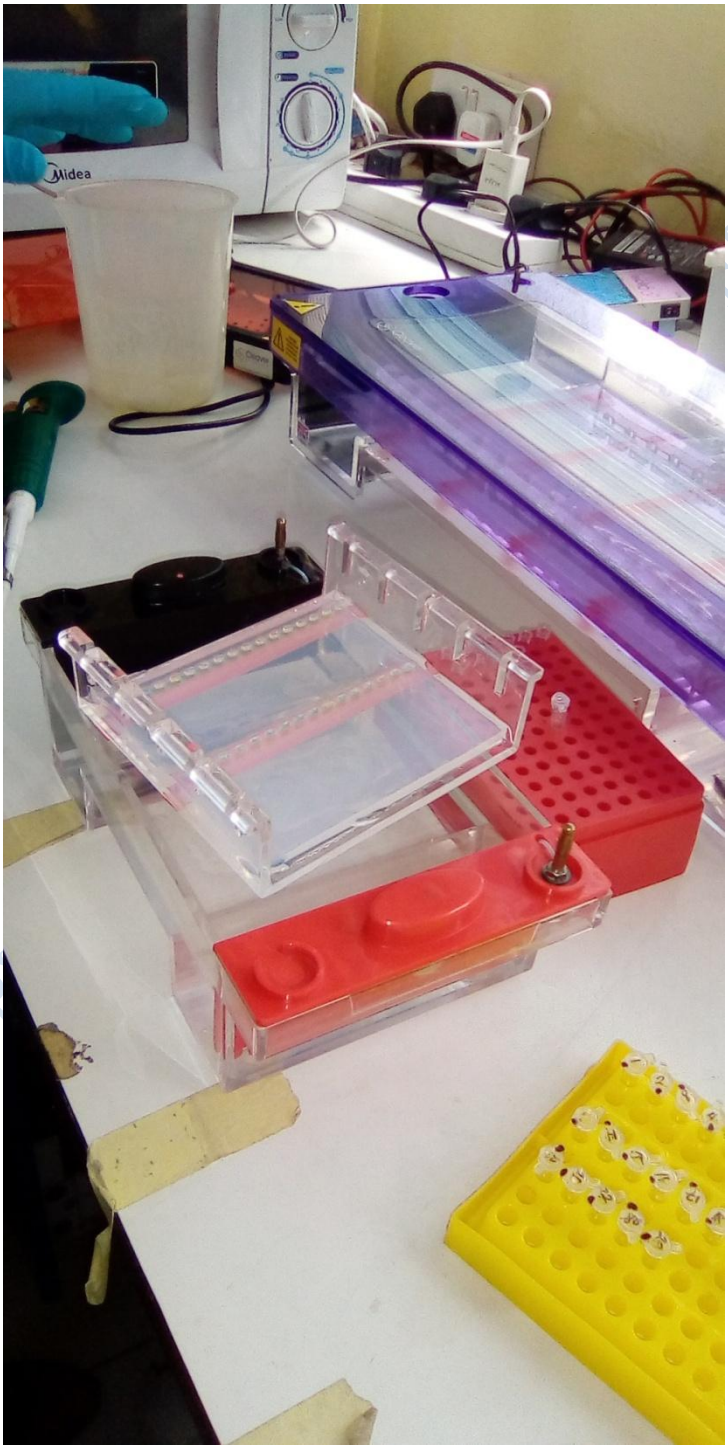
Appendix VII

PCR device.

Appendix VIII

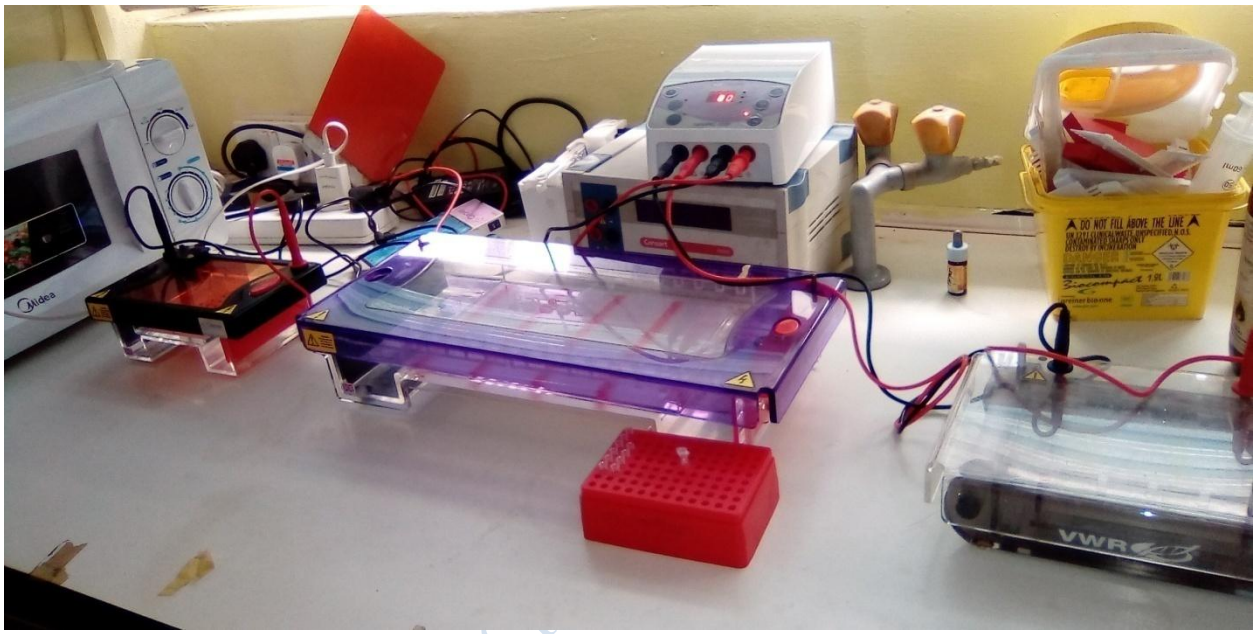
Agarose gel on Electrophoresis machine.

Appendix IX



DNA loaded agarose gel for electrophoresis.

Appendix X

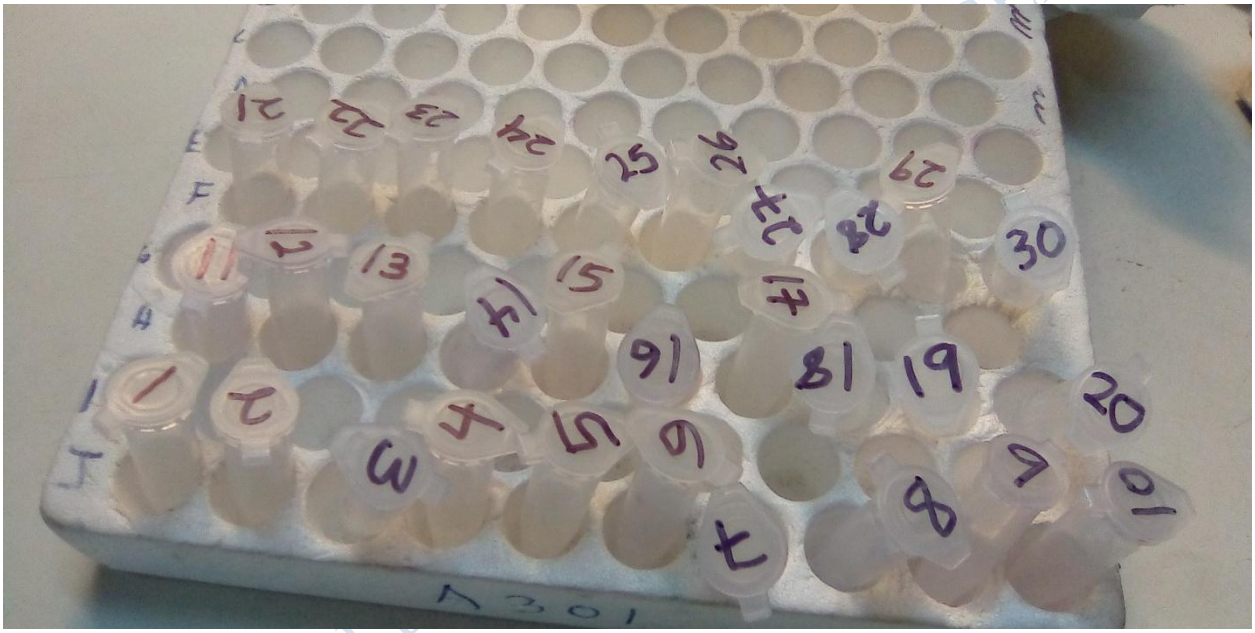


Electrophoresis machine.

Appendix XI

DNA in Eppendorf tubes

Appendix XII

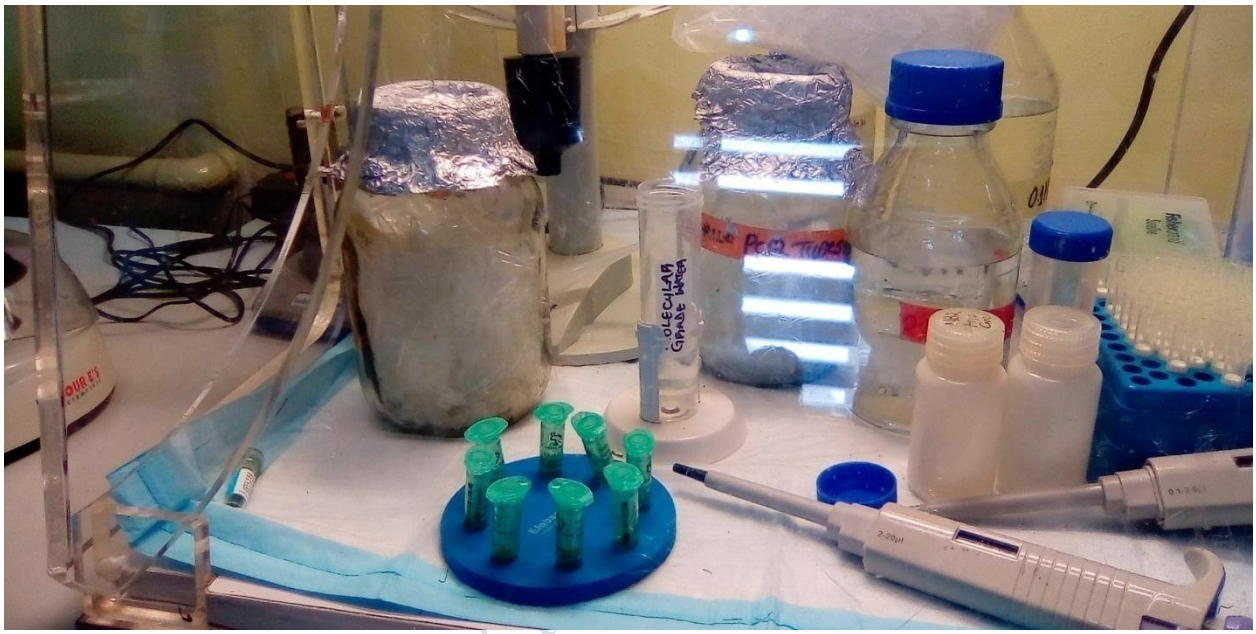


Crude DNA lysate

Appendix XIII

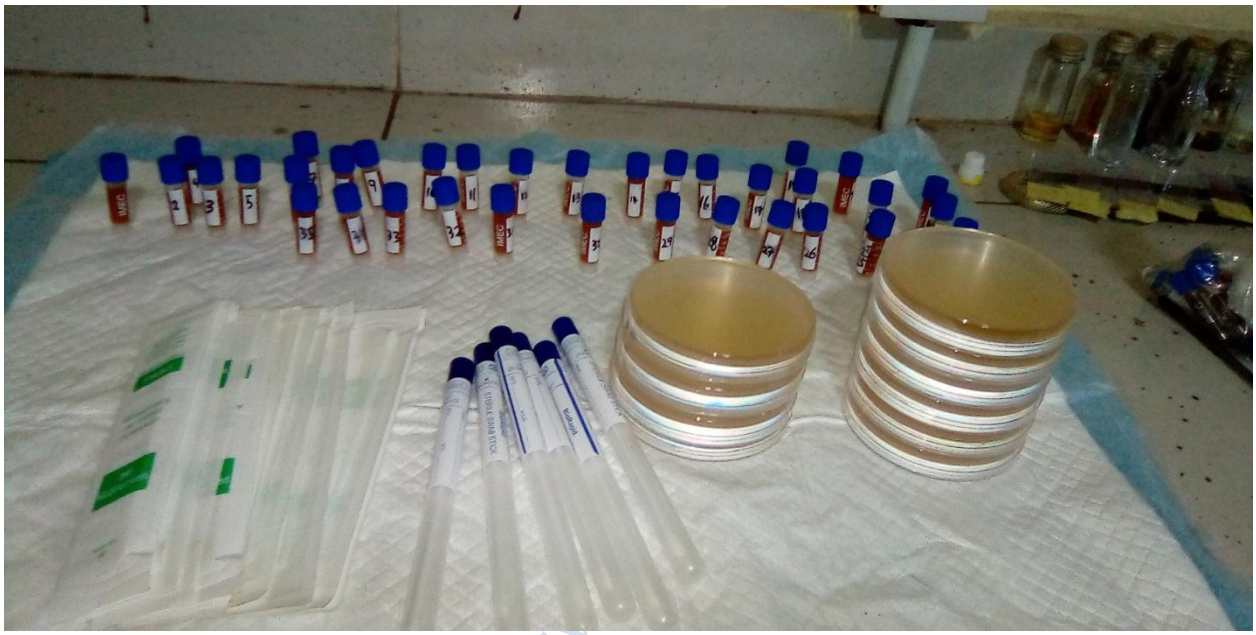
Biobase PCR machine

Appendix XIV



Primers under UV light

Appendix XV

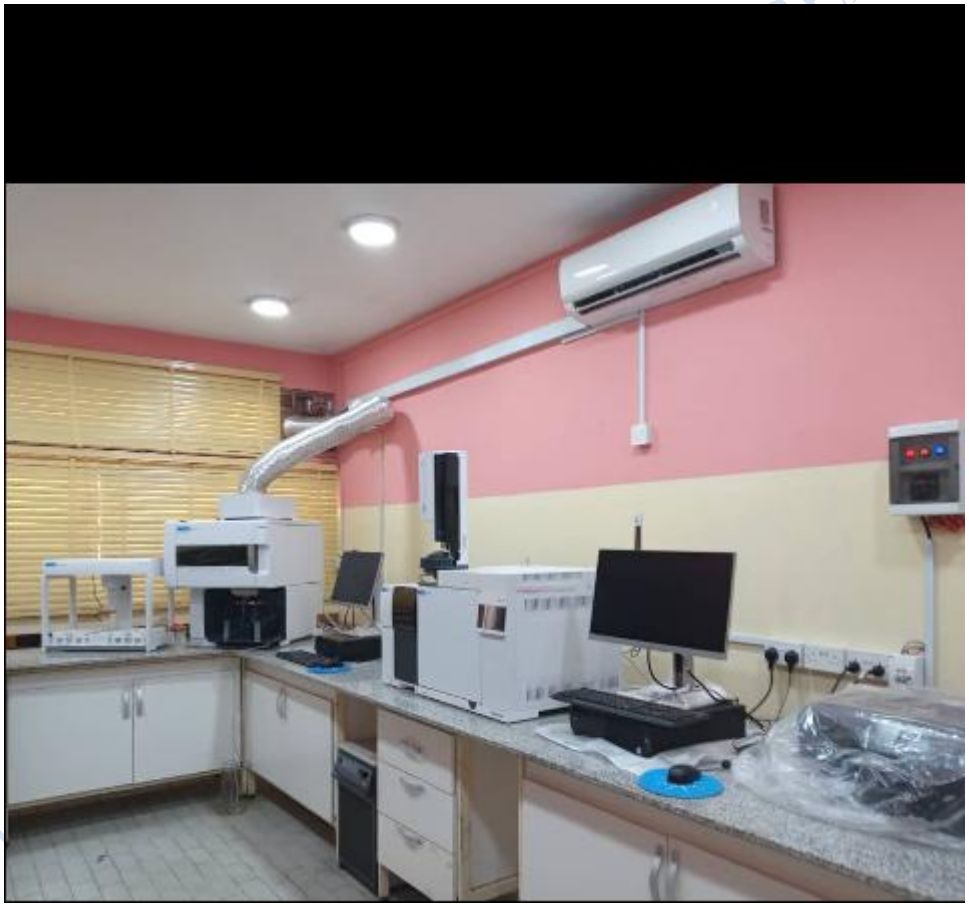


SDA plates

Appendix XVI

PCR device with monitor

Appendix XVII



PCR laboratory for molecular analysis

Appendix XVIII

DNA extraction process

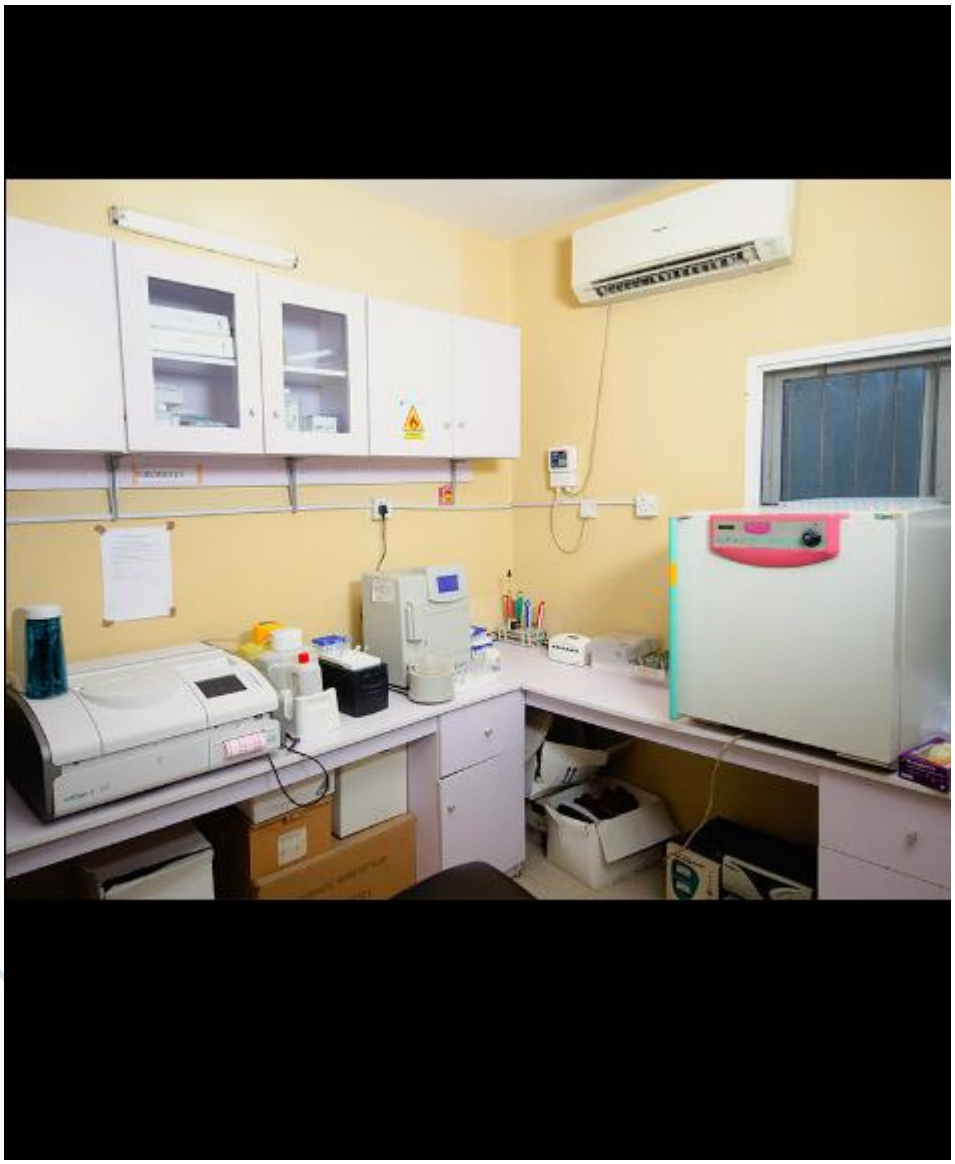
Appendix XIX

Microbiology research laboratory at Lead City University

Appendix XX

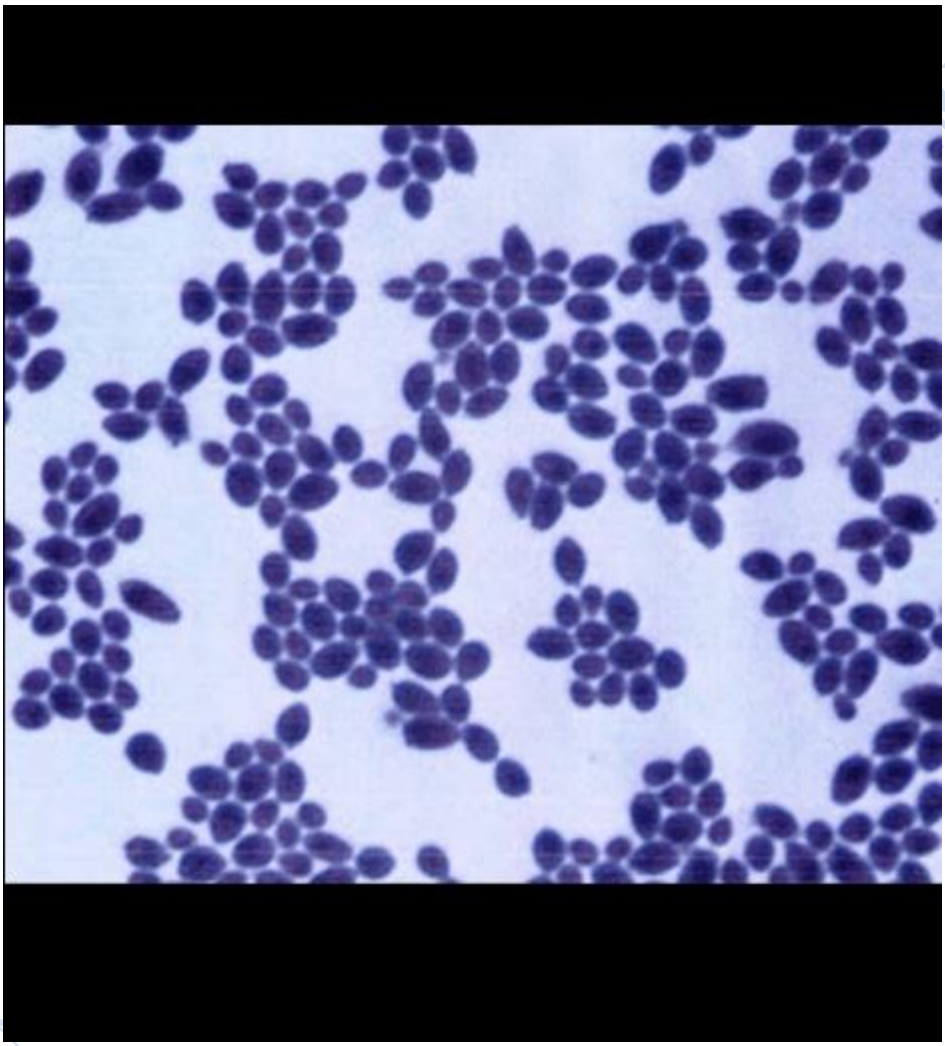
Microbiological routine laboratory

Appendix XXI



DNA consumables and processing room.

Appendix XXII



Yeast cells stained by Gram staining method.

Appendix XXIII

***Candida* species on Chromogenic agar**

Appendix XXIV

Weighing balance (analytical)

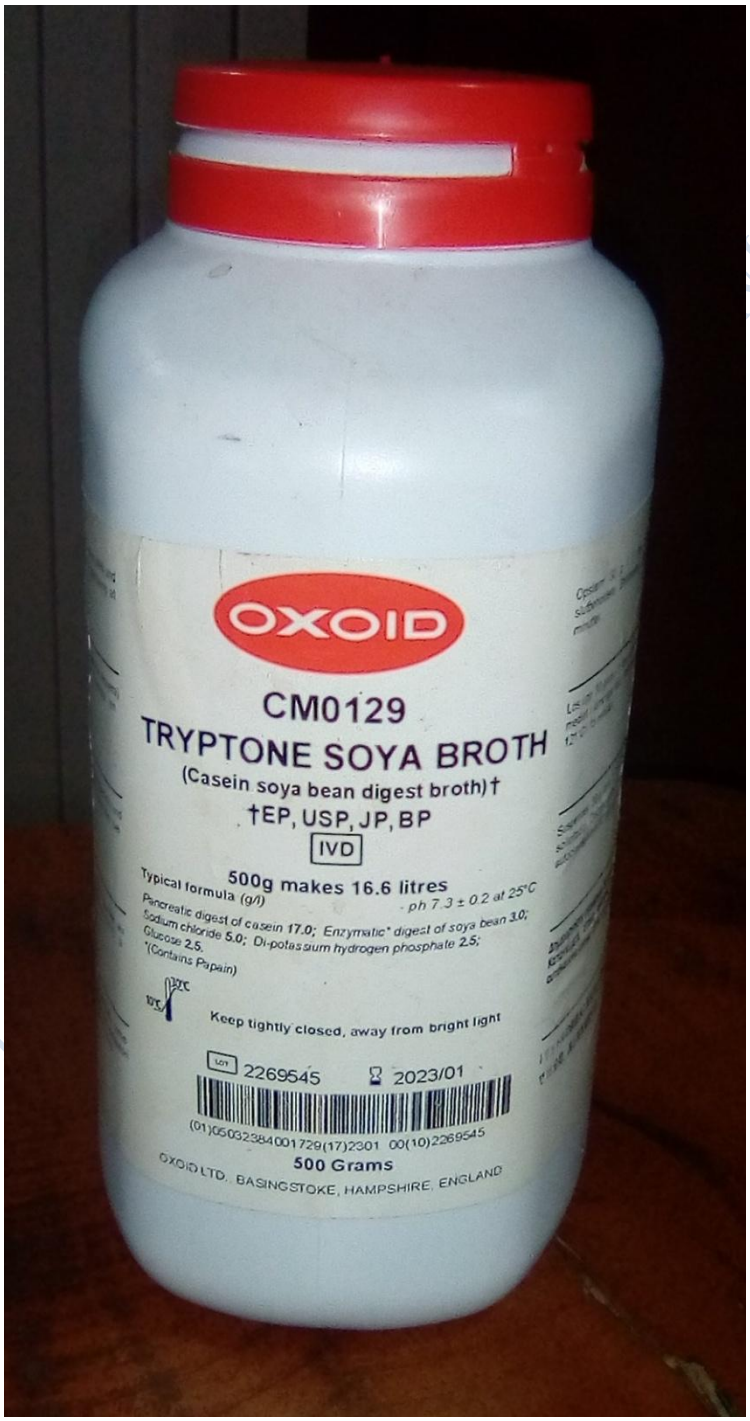
Appendix XXV

Autoclave machine

Appendix XXVI

Light Microscope in Microbiology Research Lab of Lead City University

Appendix XXVII

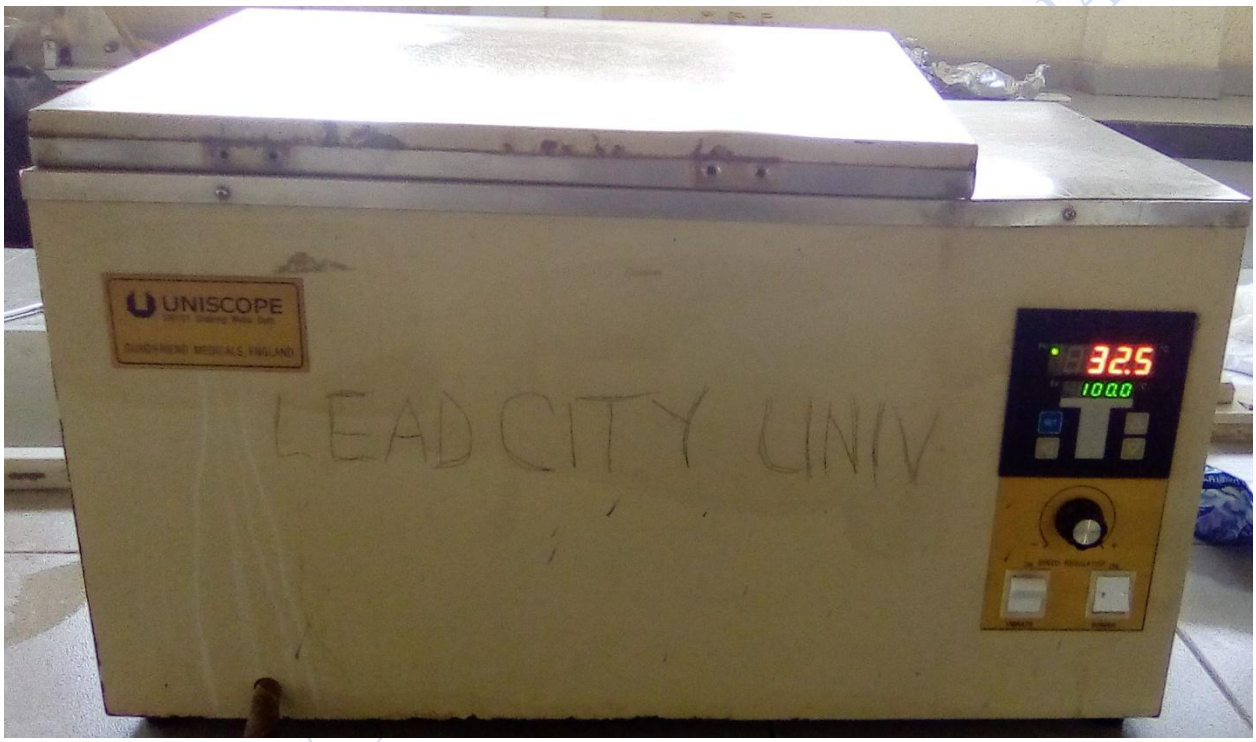


Tryptone Soya broth

Appendix XXVIII

Incubator

Appendix XXIX



Hot water bath

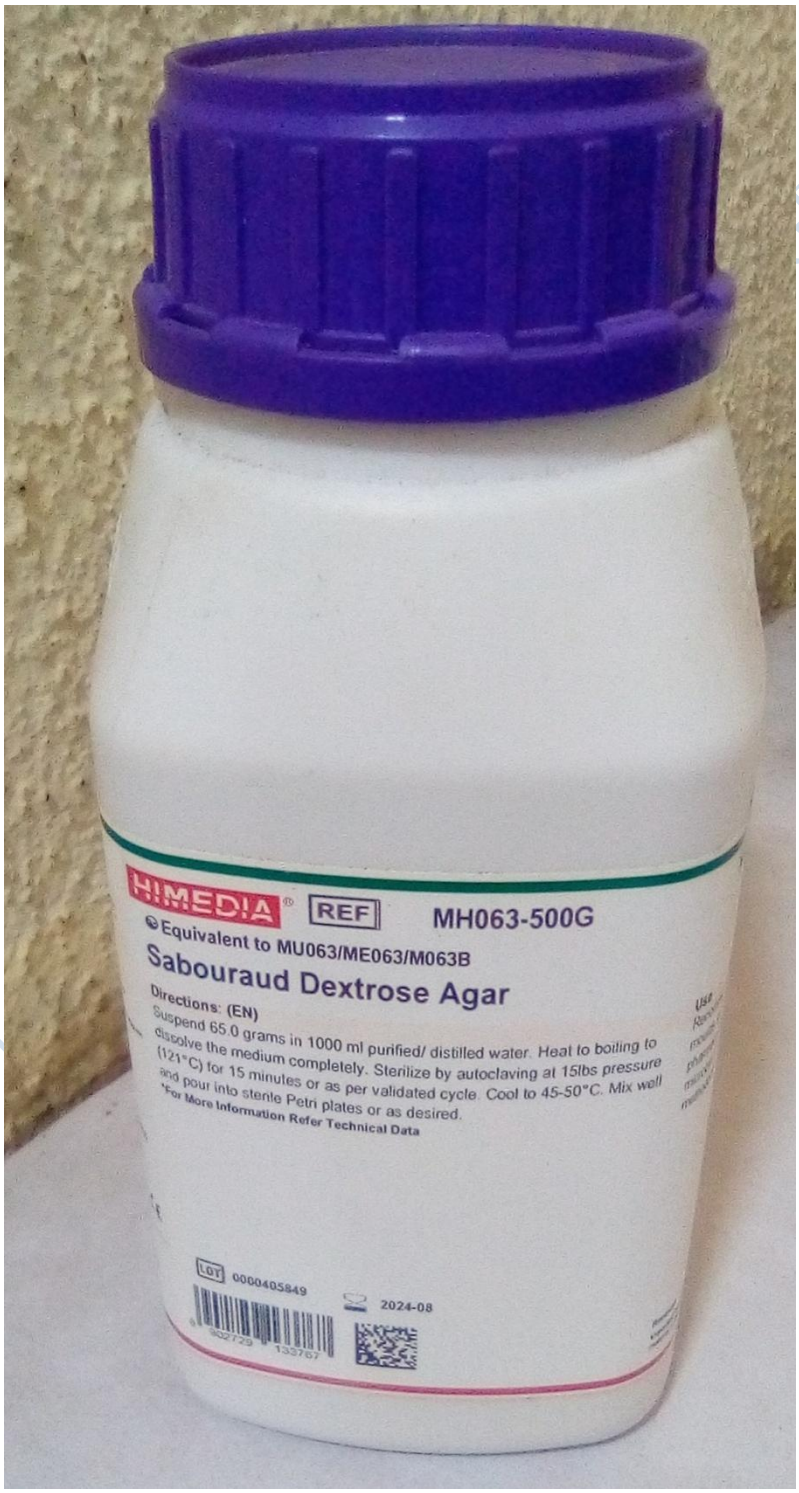
Appendix XXX

Laboratory incubator

Appendix XXXI

The Novel CHROMagar™ Candida Plus by CHROMagar™

Appendix XXXII

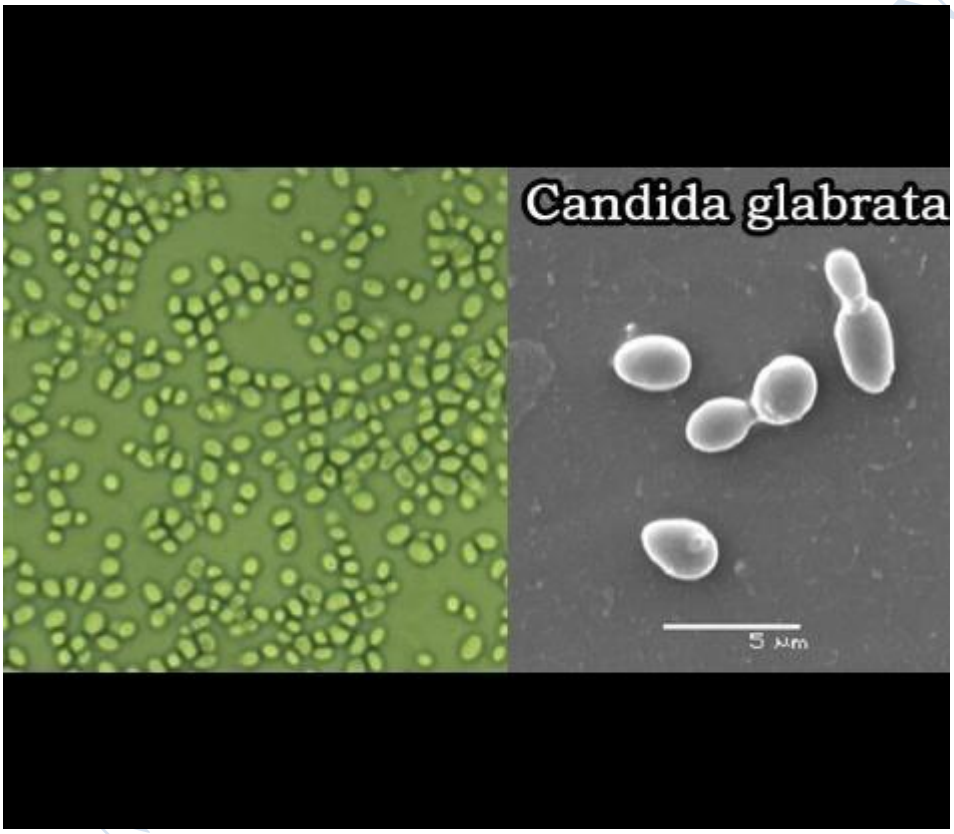


Sabouraud Dextrose Agar by HIMEDIA

Appendix XXXIII

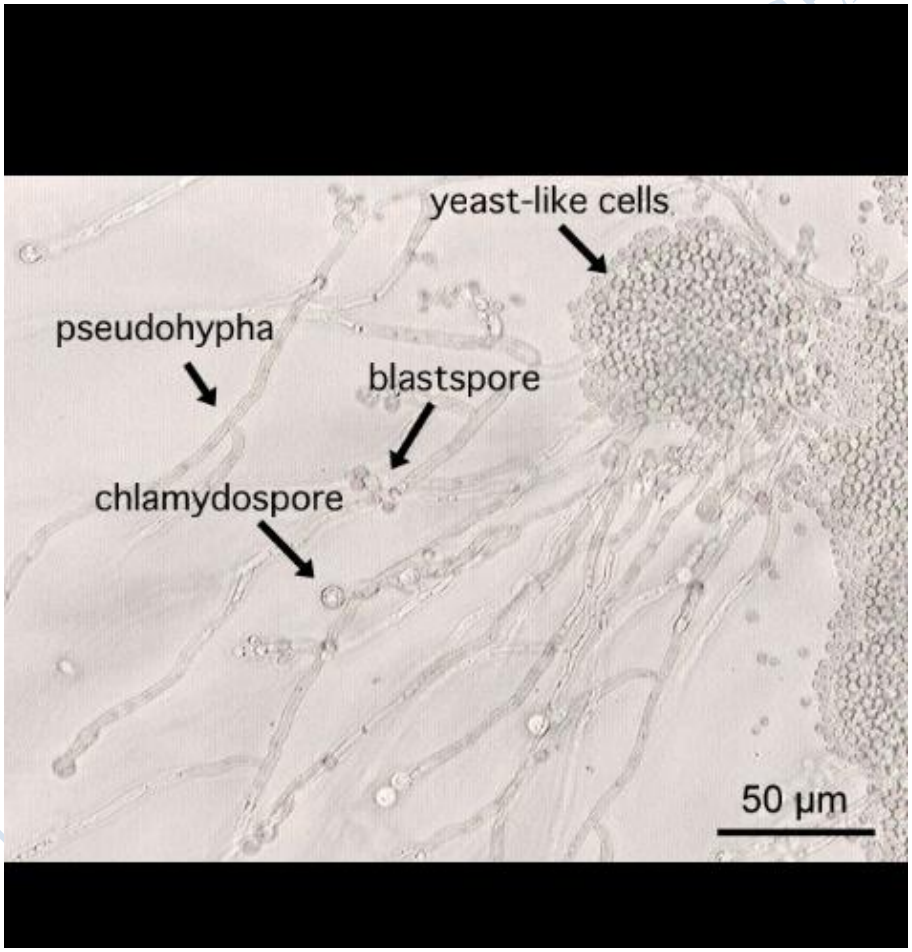
Candida **growth on Sabouraud Dextrose Agar**

Appendix XXXIV



Microscopic view of Candida specie

Appendix XXXV

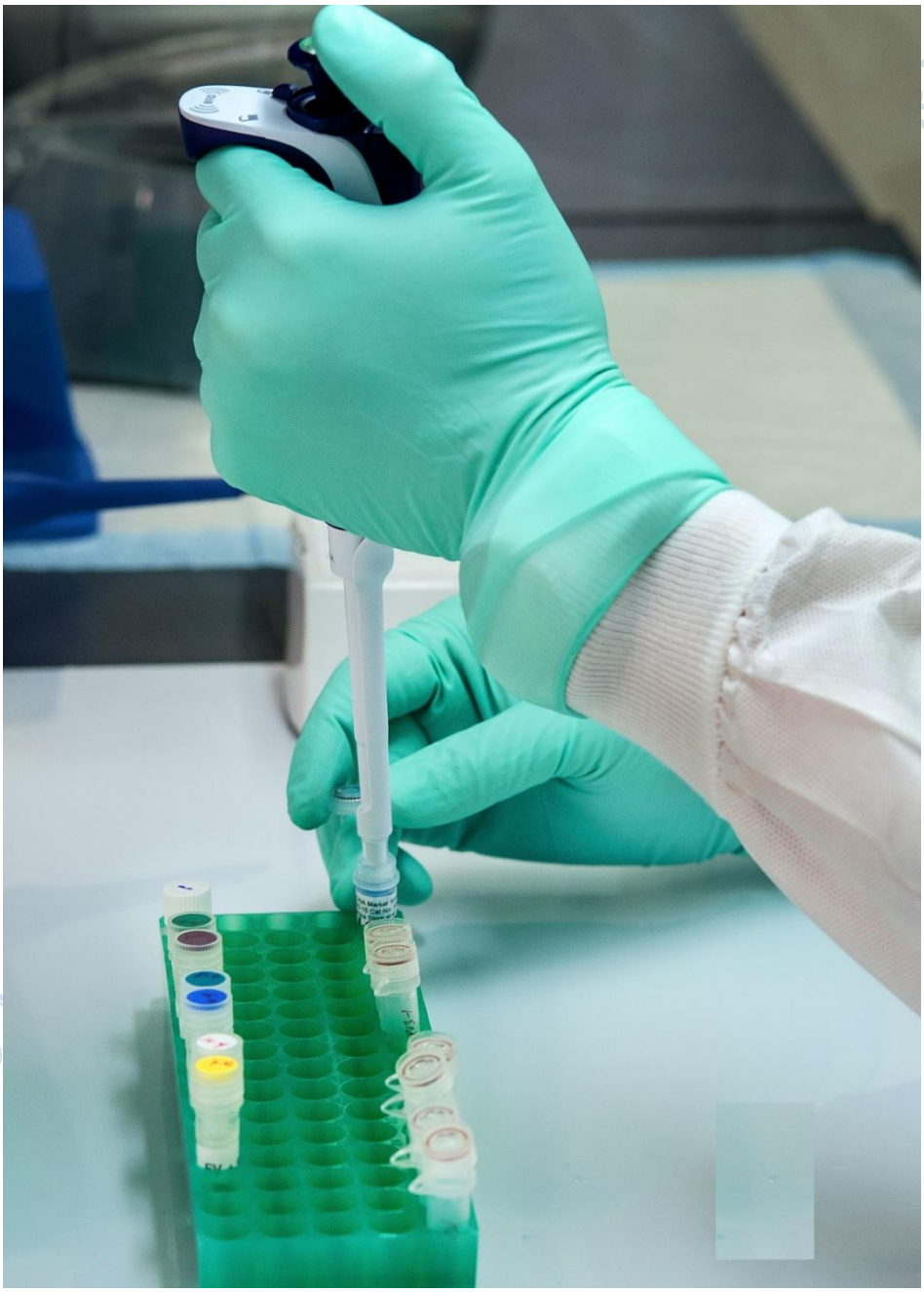


Microcopic forms of fungi

Appendix XXXVI

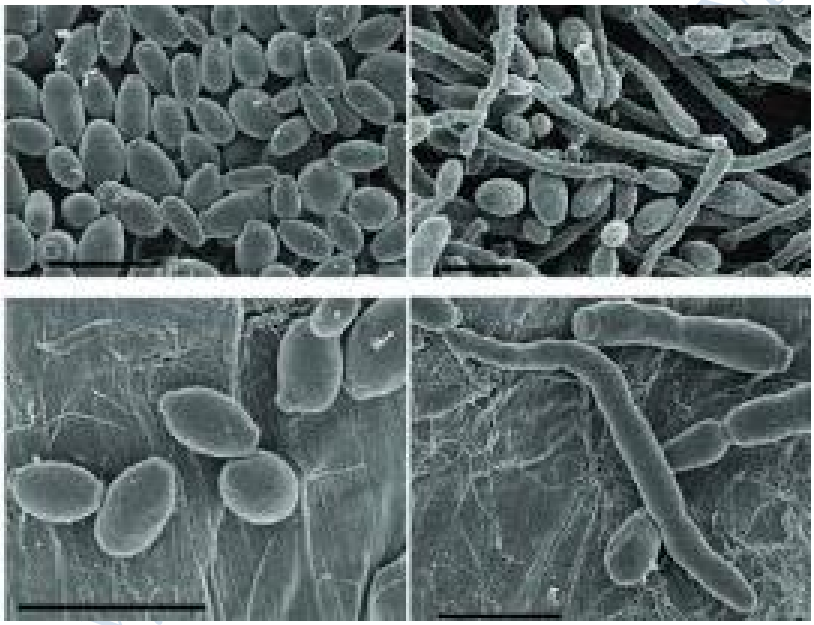
Washhand basin in the molecular laboratory

Appendix XXXVII



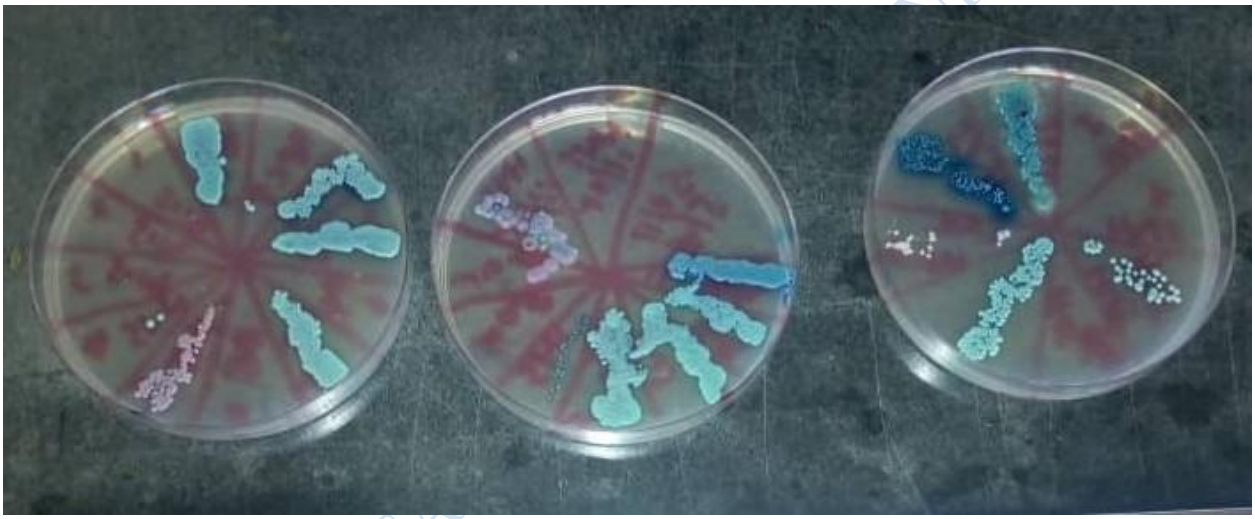
Mixing of primer sequences

Appendix XXXVIII



Typical Fungal cells

Appendix XXXIX



***Candida* pathogen on Chromagar™ Candida Plus**

Appendix XL

A contaminated Chromagar Candida Plus

Appendix XLI

Biochemical reagents rack

Appendix XLII

Molecular analysis room

Appendix XLIII

Molecular PCR device setup

Appendix XLIV

Picking out containments on Chromagar™ Candida Plus

Appendix XLV

Stacking of poured Chromogenic agar plates

Appendix XLVI

Setting up positive controls

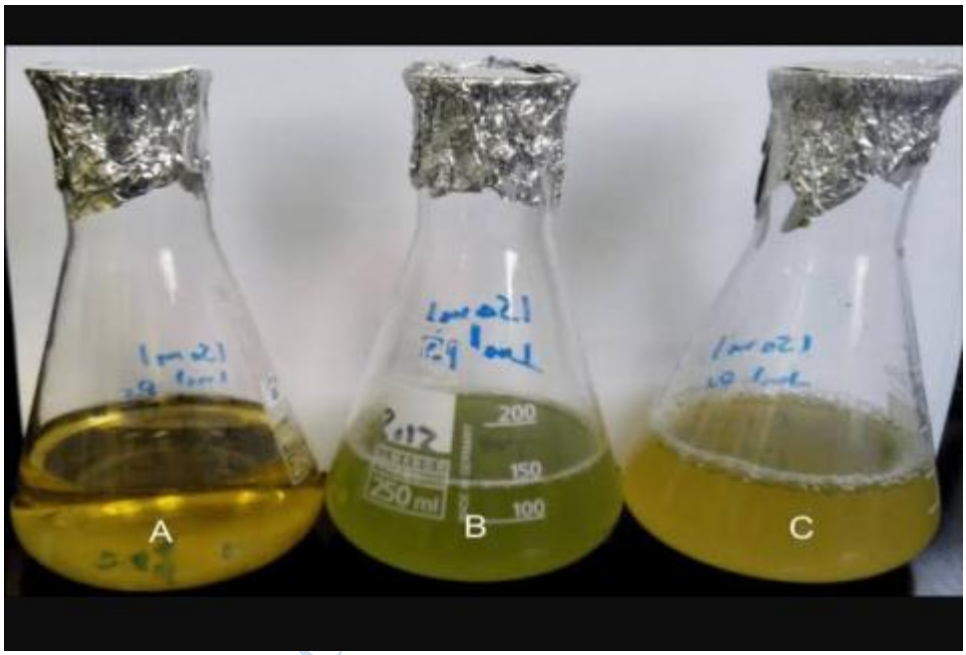
Appendix XLVII

Setting up negative control

Appendix XLVIII

Autoclaved SDA media

Appendix XLIX



Sterilized Chromagar™ Candida Plus, Tryptone Soya broth and SDA

Appendix L

Unsterilized media

Appendix LI

Contaminated Tryptone Soya broth

Ethical approval

Bio-data

Name:	Odubunmi Oluwatosin Ayobami
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Accepted manuscript for publication

Review Article: "*Candida auris* an emerging nosocomial Candida specie: The challenges in laboratory isolation, identification and recommendations for identification in economic challenged countries" Odubunmi O.A, Olayemi I.O & T.Y. Raheem. *Journal of Biomedical and Allied Research, 2021.*

_____ _____

Signature **Date**

University Compliance Certification

This is to certify that the thesis by **Oluwatosin AyobamiOdubunmi** with Matric no LCU/PG/001069 in the department of **Biological Sciences**, Faculty of Natural and Applied Sciences, Lead City University, is in full compliance with the approved university format and style.

_____ _____

Signature **Date**