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THE PREVALENCE OF METHİCİLLİN RESİSTANCE STAPHYLOCOCCUS AUREUS AMONG GENERAL POPULATİON İN NORTH CYPRUS

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MSc. THESIS

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I now certify that all data, records, analyses, and findings in this thesis were gathered in compliance with the academic standards and moral obligations set forth by the Near East University Institute of Graduate Studies. I further declare that, in accordance with these guidelines and standards of behavior, I have properly referenced and cited any data and information that is not unique to this work.

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Noor Nassar

Abstract

The Prevalence of Methicillin Resistance *Staphylococcus aureus* Carriage Among General Population In Northern-Cyprus

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Since Methicillin-resistant *S. aureus* (MRSA) is resistant to most medicines, it poses a great challenge. Therefore, prompt and accurate MRSA diagnosis is crucial to prevent treatment failure and control the spread of this bacterium. In this study, *S. aureus* was determined from nose swabs taken from the general population in Northern Cyprus. The study also aims to reveal the organisms' resistance pattern and compare the efficacy of conventional Cefoxitin disc diffusion methods and MRSA chrome agar methods for the discovery of MRSA. Methicillin resistance in *S. aureus* was assessed in all cases using Cefoxitin disk diffusion and MRSA chromagar *S. aureus*. Using CLSI recommendations, Cefoxitin disk diffusion was used to measure antibiotic sensitivity. The Pearson chi-square test was the testing method for the results in this study, with an SPSS version 27 for all statistical analyses. A P value of 0.005 was considered significant. Nine (6%) out of 150 were isolated as MRSA. The sensitivity and specificity of Cefoxitin disk diffusion techniques were 100% and 100%, respectively, while HiCrome agar-MRSA showed 100% and 50%, respectively. Compared to the HiCrome agar MRSA method, the Cefoxitin disk diffusion method provides a greater sensitivity and specificity for MRSA identification. The latter can be utilized for MRSA screening because it has strong sensitivity and specificity and can detect most MRSA.

Key words: MRSA, MSSA, cefoxitin, mec a gene, *S. aureus*

Özet

Kuzey Kıbrıs'ta Genel Popülasyonda Metisilin Direnci *Staphylcoccus aureus* Taşıyıcılığının Yaygınlığı

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Metisiline dirençli S. aureus (MRSA) çoğu ilaca dirençli olduğundan büyük bir zorluk teşkil etmektedir. Bu nedenle, tedavi başarısızlığını önlemek ve bu bakterinin yayılmasını kontrol etmek için hızlı ve doğru MRSA tanısı çok önemlidir. Bu çalışmada Kuzey Kıbrıs'taki genel popülasyondan alınan burun sürüntü örneklerinde tipik teknikler kullanılarak S. aureus belirlendi. Çalışma aynı zamanda organizmaların direnç paternini gözlemlemeyi ve MRSA keşfinde geleneksel Sefoksitin disk difüzyon yöntemleri ile MRSA krom agar yöntemlerinin etkinliğini karşılaştırmayı amaçlamaktadır. S. aureus'taki metisilin direnci tüm vakalarda Sefoksitin disk difüzyonu ve MRSA chromagar S. aureus kullanılarak değerlendirildi. CLSI önerileri kullanılarak antibiyotik duyarlılığını ölçmek için Sefoksitin disk difüzyonu kullanıldı. Microsoft Office Excel'de saklanan verileri değerlendirmek için bir p değeri anlamlılık testi ve diğer istatistiksel teknikler kullanıldı. 150 kişiden dokuzu (%6) MRSA olarak izole edildi. Sefoksitin disk difüzyon tekniklerinin duyarlılığı ve özgüllüğü sırasıyla %100 ve %100 iken HiCrome agar-MRSA sırasıyla %100 ve %50 gösterdi. HiCrome agar MRSA yöntemiyle karşılaştırıldığında Sefoksitin disk difüzyon yöntemi, MRSA tanımlaması için daha yüksek hassasiyet ve özgüllük sağlar. İkincisi, güçlü bir duyarlılığa ve özgüllüğe sahip olduğundan ve çoğu MRSA'yı tespit edebildiğinden MRSA taraması için kullanılabilir**.**

***Anahtar Kelimeler*:** MRSA, MSSA, cefoxitin, mec a gene, *S. aureus*

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CHAPTER I

Introduction

Overview

Staphylococcus aureus is a round, non-motile, spore-forming, gram-positive bacteria. Certain strains of the bacteria are capsulated because penicillin releases the enzyme penicillinase. 94% of *S.aureus* strains are notably resistant to penicillin and its derivatives. Methicillin resistance in some strains of *S.aureus* has been recognized as MRSA (Bouiller *et al*., 2020). Clinical methicillin resistance could be ascertained by Cefoxitin resistance as well as the PCR-based mecA gene. This particular form of antibiotic resistance is caused by the penicillin-binding protein (PBP-2A), which is mostly expressed by the mecA gene (Bouiller *et al*., 2020).

S. aureus virulent zoonotic biovars known as MRSA satisfied certain requirements, including being methicillin and Cefoxitin-resistant. It is possible to differentiate between methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) using a wide range of phenotypic and molecular features. MRSA regularly displays a multidrug-resistant pattern to penicillin as well as other variable antimicrobial classes such as aminoglycosides, tetracyclines, macrolides, fluoroquinolones, and lincosamides (Bouiller *et al*., 2020).

MRSA is not just a nosocomial bacterium, it is also recognized as the primary cause of community-acquired infections (CA-MRSA) and hospital-acquired infections (HA-MRSA). Globally, the mortality rate of CA-MRSA infections has increased. Genetically, CA-MRSA mainly differs from HA-MRSA in that it produces cytotoxin and Panton-Valentine Leukocidin (PVL). People outside of the healthcare industry are banned from contacting CA-MRSA strains, which typically result in minor infections such as skin and soft tissue infections (Ceballos *et al*., 2019).

However, it was revealed by current epidemic-molecular studies that multiple people in healthcare settings may be affected by CA-MRSA. Livestock-associated MRSA, often known as LA-MRSA, is a different kind of MRSA that impacts a range of household animals. The rise of MRSA in livestock is caused by the widely used

and incorrect use of antibiotics in the veterinary sector. This suggests that MRSA, which causes infections in humans, is permanently stored in the afflicted animal (Ceballos *et al*., 2019).

Research Purpose

This study aims to investigate the prevalence of methicillin resistance *Staphylococcus aureus* carriages of Northern Cyprus

The following sub-goals may flow from this main objective including:

1-To examine and provide a numerical depiction of the prevalence of Methicillin-Resistant *Staphylococcus aureus* carriages of Northern Cyprus

2- Investigating the spread of MRSA in various groups and environments

3- Studying the prevalence, distribution, and transmission patterns of MRSA carriers in Northern Cyprus

Research Importance

Understanding the incidence of MRSA in a given neighbourhood is crucial to minimizing the impact of this antibiotic-resistant disease on public health. If MRSA infections are prevalent, the community and health research help to understand the global circulation of MRSA, which is a global health concern. This information is essential for creating plans to stop MRSA from spreading and stop it from appearing in new areas that would be severely impacted.

Research Questions

This research revolves around these questions:

1- Are there any demographic factors, such as age, gender, or socioeconomic level, which influence the frequency of MRSA in Cyprus?

2- What is the number of MRSA colonizers in Northern Cyprus?

3- How to create effective control methods? Is it necessary to comprehend the prevalence and distribution of MRSA in various populations and areas?

4- What is the confirmatory test of MRSA in in-vitro identification?

5- What effects do behavioral and social factors have on MRSA transmission and prevalence?

Limitation of the Study

The fact that the study's sample isn't representative of the population as a whole raises the possibility of sampling bias. If the study only looks at a given age range or healthcare setting, for instance, the conclusions might not apply to a larger population.

The degree to which the diagnostic methods used for MRSA identification are sensitive and specific may affect the accuracy of prevalence estimates. Inconsistent results could arise from variations in laboratory techniques.

Definition of Key Terms

S. aureus harmlessly lives on the skin but if it gets inside the body, immediate treatment with antibiotics is needed to avoid the threat of a serious infection.

Cefoxitin Antibiotics

Methicillin resistance can be quickly and affordably screened for using the Cefoxitin disk test. Since Cefoxitin can sometimes be a more accurate sign of resistance than methicillin it is used in place of the antibiotic (Butler *et al.,* 2018).

MRSA Colonizer

A person who has Methicillin-resistant *S. aureus* (MRSA) colonizer on their skin or in their nasal passages but does not exhibit symptoms of an active infection is known as MRSA carrier. In certain people, MRSA can colonize the body without making them sick; these people are called carriers (Butler *et al.,* 2018).

Mec A gene

It is a gene that enables bacteria to resist antibiotics like methicillin, penicillin, and other antibiotics that work similarly to penicillin (Butler *et al.*, 2018).

HA-MRSA

According to CDC, Hospital-Acquired MRSA (HA-MRSA) as an MRSA infection that occurs in people who have recently undergone dialysis by using a long-term indwelling medical device, who have been treated or had surgery within the past year, or who live in a long-term care facility (Butler *et a.*, 2018).

CA-MRSA

The term "Community-Acquired MRSA Infections" (CA-MRSA) refers to MRSA infections in healthy people who have not recently had surgery or dialysis or been admitted to the hospital (Butler *et al.,* 2018).

CHAPTER II

Literature Review

Staphylococcus aureus

Staphylococcus is genus that now has 81 species, and many subspecies of species in the genus are mostly commensals or opportunistic pathogens that live alongside mammals. Both veterinary and medicinal relevance can be found in many species of Staphylococcus.

S. aureus is most crucial for human pathogenicity (Ceballos *et al*., 2019). *S. aureus* is named after two Greek words: staple, meaning bunch, and 'kokkos', meaning grapes. The term" bunch of grapes" refers to what is observed under a microscope (Ceballos *et al*., 2019).

Staphylococcus aureus, which translates to "Golden cluster seed," is the source of the term "golden staph" *S.aureus* is a gram-positive, coccus-shaped, non-motile, spore-forming, opportunistic bacterium which produces a lot of enzymes such as catalase, nucleases, coagulase, lipases, collagenases, and B-lactamase (Shiadeh *et al*., 2021). It generates colonies on different culture media in different colors: green colonies on blood agar, yellow colonies on Mannitol salt agar, and golden or grey colonies on chromogenic agar when examined under a microscope. *S.aureus* resembles spherical seeds grouped in bunches, indicating that it grows on multiple planes (Shiadeh *et al*., 2021).

Many different types of infections, from minor to life-threatening, are brought on by *S. aureus.* Because of its commensal and opportunistic traits, it can colonize a variety of places on the body surfaces of humans and animals. Urinary tract, skin, and mucosa, gastrointestinal tract, and most commonly the respiratory tract's anterior nares all common habitats for *S. aureus* (Butler *et al.,* 2018).

Numerous virulence factors can be produced by *S. aureus* including different kinds of proteins, Toxin, enzymes, and other compounds with a high pathogenicity. Fibronectin-binding protein and protein A are produced by *S. aureus* and they both help the bacteria stick to and colonize the cell surface. *S. aureus* produces a variety of toxins including hemolysin, enterotoxins beta, gamma, and Panton-Valentine Leucocidin (PVL) toxins, exotoxin *S. aureus* infections spread as a result of all of

these factors. This can lead to serious necrotizing infection and bloodstream infections in people (Parveen et al., 2020)

Emergence and Types of MRSA

The bacterium was initially identified as "*S. aureus"* in 1881 after being separated from a pus specimen that was used before the discovery of penicillin by Radetsky (1996), there was a documented rise in *S. aureus* infection-related mortality with case fatality rates reaching 90%. These infections continued to cause infections until the 19th century (Dadashi *et al*., 2018). Subsequently, *S. aureus* produces B-lactam enzyme, which hydrolyzes penicillin's B-lactam in which it performance the antibiotics ineffective. The resistance develops in *S aureus* quickly after the antibiotic's discovery (Algammal, 2020).

Then, in 1950, Methicillin, a different antibiotic, was discovered and shown to be long-lastingly effective against *S. aureus.* Unfortunately, these antibiotics have become useless due to the bacteria's substantial resistance to them. *S. aureus* species known as the methicillin-resistance strain (MRSA) was found to be resistant to this antibiotic at a higher percentage. Staphylococcal cassette chromosome Mec (SCC) genes, including the mecA gene, are acquired by methicillin-susceptible *S. aureus* (MSSA) by horizontal gene transfer between bacteria. This is where molecular foundation of MRSA evolved (Kourtis, 2019).

The methicillin-susceptible *S. aureus* (MSSA) bacteria acquire genes like mecA gene from the staphylococcal cassette chromosome mec (SCCmec), a sizable mobile genetic element, through horizontal gene transfer. This is where the molecular foundation of MRSA developed. The mecA gene's synthesis of penicillin-binding protein (PBP-2A) resulted in resistance to all B-lactam antibiotics (Kourtis, 2019).A study done in 1961 indicated that out of 50 staphylococci samples, 18 of them had methicillin resistance, indicating a significant percentage of MRSA (36.0%). It was found that these isolates were capable of maintaining hemolytic and coagulase activities. Methicillin resistance in *S. aureus* varied throughout isolates, making MRSA diagnosis challenging when it was first discovered. In a study, just three isolates out of 5000 *S. aureus* samples analyzed were identified as MRSA in the research. Because of this, the majority of the bacterial cells seen in heterogeneous strains each have a strong resistance and vulnerable to methicillin (Lim, 2019).

Nevertheless, when B-lactam antibiotics are present Increasing the amount of sugar or sodium chloride (NaCl) in the culture media may promote the expression of the resistance phenotype (Ou *et al.*,2018). For many years, MRSA has been linked with nosocomial infections and MDR infections that cause infections in hospitals and other healthcare workers. The percentage of MRSA infections has significantly increased over the past thirty years. (Ou *et al.*,2018).

Healthcare-associated (HA-MRSA) is a unique strain of MRSA that has spread and become endemic in developed countries. It is the main cause of pulmonary septicaemia and skin infections. (Dhungel *et al.*,2021). It was reported to be a highly virulent MRSA strain that spread rapidly toward the end of the 1990s. It could infect both healthy and young people (Parveen *et al.*, 2020).

Epidemiology and Prevalence of MRSA

The global emergence and transmission of the bacteria are the main concerns of MRSA epidemiology (Lozano *et al.*, 2020). There are two known ways that MRSA spreads: either through the dissemination of clones that already exist between humans and animals, or from humans to humans or animals to humans, or through the acquisition of SSCmec elements through horizontal gene transfer. MRSA is one of the most common nosocomial infections that are currently reported to be more endemic in hospital settings (Crespo-Piazuelo *et al* 2021).

As per the CDC's statement, MRSA is recognized as a serious threat to public health because of its growing occurrence in hospitals and, communities as well as its ability to spread between animal and human, resistance, therapeutic, and infection rates concerns (Gittens-St Hilaire *et al*., 2020). The yearly health costs associated with MRSA infections are estimated to be $3 billion on average. Recently, CA-MRSA has also become more prominent as a pathogen (Sangwan *et al.*, 2021). It is known that MRSA mostly causes soft tissue infections and skin infections, which can result in bacteremia and higher death rates of 15-60% (Holm *et al*., 2021). Recently, there has been an increase in the incidence of HA-MRSA, with differences observed amongst the nations. For instance, Portugal has a higher prevalence rate of 58.4 percent in 2013 (Nickol *et al*., 2019), 46 percent came from India in 2009 (Meliton *et al.*, 2023), 52 percent from Pakistan in 2017 (Joseph *et al.*, 2020), 45 percent from china from 2015 to 2017 (Ayoud *et al.*, 2020) and 38.9 percent shows

Norway from 2008 to 2016 but while HA-MRSA is becoming more common in many nations (Amati *et al*., 2020).

MRSA prevalence is also declining in many countries as 4.6 percent in Germany (Habib *et al*., 2022), 5 percent in Texas (Paudel *et al*., 2022), 19.1 percent in Mexico (*Singh et al*., 2023), 15.1 percent in Austria (Htwe *et al*., 2021), and 26 percentage from Italy (Ahmed, 2020).

Similarly, rising and falling trends in MRSA prevalence have also been observed for CA-MRSA in many nations, including 79% in Japan (Hansen *et al*., 2020), 84.9% in Australia (Craft *et al.*, 2019), 64.7% from India (Tran and Dait, 2021), 61% from Norway (Lim and Wen, 2019), 44.3% from Iran (Crespo-piazze *et al.*, 2021) with 16% prevalence from Egypt (Marulasiddeshwara *et al*., 2020) and 1.7% from China (Silva and Vanessa, 2020).

MRSA Pathophysiology

S. aureus is a commensal as well as pathogenic bacteria which typically inhabit the nasal cavity of animal and people. Moreover, it can invade the gastrointestinal tract, groin, and axillae system. The pathogenesis of infections involves several major processes, including abscess formation systemic infection, colonization, infection start, regulation pathogenicity, and adaptation through virulence factors. When host's defences become weak by physical disturbance or other illnesses, colonization increases the likelihood of bacterial infection (Shoaib *et al*., 2023).

Since MRSA contain a variety of potential virulence factors which includes several surface proteins known as "microbial surface components recognizing adhesive matrix molecules (MSCRAMMs). These proteins attach to host cell, fibronectin, collagen fibers, and fibrinogen which in turn attacks host tissues. Infections of the prosthetic limbs, bones, joints, and endovascular system can result from this circumstance (Galar *et al*., 2019). By avoiding the antimicrobials effect and the host immune system *S. aureus* can form biofilm on prosthetic surface as well as the host, which enables it to cling to those surfaces as well as the host (Galar *et al*., 2019).

Additionally, *S. aureus* is capable of producing small colony variations (SCVs) which can lead to recurring and persistent infections. This anti-phagocytic

microcapsule (type 5 or 8) is another defence mechanism seen in *S. aureus* (Galar *et al*., 2019).

Nonetheless, the PBP2-a protein expressed by the mecA gene and linked to B-lactam antibiotic resistance is assumed to have a direct role in immunopathology during MRSA infection. MRSA strains are more likely to survive than MSSA bacteria because PBP2-a produced peptidoglycan which has difficult attaches to peptidoglycan cross-linking with B-lactam antibiotics. (Bendre andratnamale, 2022).

The high virulence of CA-MRSA attributed to improved *S. aureus*-exclusive toxin production and immune system. Research has discovered that the dermonecrotic and leukocyte-lysing characteristics of *S. aureus's* PVL protein boost the pathogenicity of CA-MRSA stains (Ojala *et al,* 2023). These studies indicate the complex link between CA-MRSA and PVL (Abdullahi *et al.,* 2023). Another report showed CA-MRSA to have high concentrations of phenol-soluble modular proteins than HA-MRSA strains, which stimulate inflammation and reduce neutrophil function in bacteremia patients and mouse models (Wang *et al*., 2007).

Hospital-Acquired MRSA

Patients who are elderly or immunosuppressed as a result of extended use of broad-spectrum antibiotics poses a significant risk to HA-MRSA infections (Poolman *et al*., 2018). The explanation behind the spread of hospital-acquired infections is the resistance HA-MRSA to nearly all β-lactam medications (Mehta *et al.,* 2020). In healthy individuals, CA-MRSA is more likely to be present than HA-MRSA. Because of their frequent contact, it is also more common among day care facilities, prisoners, athletes, and military personnel (Hamer and Aseel Kadhim, 2023).

Due to its multidrug resistance, HA-MRSA is an organism that can cause several illnesses in both adults and children that are related to medical care. Individuals with weakened immune systems and those with skin wounds that could potentially transmit infections have higher infection rates (Sartelli *et al*., 2020). Dominant bacterial clones called HA-MRSA are primarily responsible for these kinds of diseases in both animals and human. The distribution of these clones varies depending on where they are located (Sartelli *et al*., 2020).

Community-Acquired MRSA

CA-MRSA can occur in the soft tissue and skin, and can occur in the bloodstream, bone, urinary system, joints, surgical sites, and lungs (Chukwueze *et al.*, 2022). However, In CA-MRSA, the primary cause of necrotizing pneumonia and septicemia in addition to being restricted to soft tissue and skin. In addition, bacteremia—a consequence of CA-MRSA causes osteoarticular infections and endocarditis. (Barbier *et al.*,2023). In 2003, researchers in Japan used methods such as spa typing, agr typing, PCR assay for virulence genes coagulase typing, and multi-locus sequence typing(MLST) to define the PVL positive CA-MRSA in children, SCC mec typing (Alidrisi *et al*, 2023). However, In Saudi Children's Hospital, there was a highly increased in CA-MRSA infections up to 29.8%, with the remaining 70.2% resulting from unknown risk variables. A study of children receiving outpatient care at King Fahad Medical City in Riyadh, Saudi Arabia between 2019 and 2020 revealed that 29.8% of cases were positive for CA-MRSA, with the remaining 70.2% being attributable to unidentified risk factors (Alidrisi *et al.*, 2023). Initially, it was believed that CA-MRSA was a nosocomial strain that had moved into houses from hospitals. On the other hand, CA-MRSA strains have clinical symptoms more similar to those of MSSA strains and, ironically they are more responsive to nonβ-lactam antibiotics than the HA-MRSA strains that are frequently seen in healthcare settings (Takadama *et al.*, 2020).

The three primary characteristics that distinguish a genetic lineage separates a CA-MRSA strain from a HA-MRSA strain, the genetic makeup of the methicillin resistance genes, in addition to PVL's presence (Foster and T. J, 2019). Based on available data, multiple unique MSSA ancestral clones that are now in circulation are integrated by SCCmec, particularly SCCmec IV, into CA-MRSA strains via a gene transfer process (Shohayeb *et al*, 2023).

Treatment Strategies for MRSA Infections

Nearly 50% of the population may be affected by bacteremia among those with established MRSA infections, which could be fatal (Bustamante *et al.*, 2023). Reduced MRSA infections may arise from MRSA prevention strategies and the use of current antibiotic therapy, both separately and in combination (Khan *et al.*, 2018).

The high fatality rate could be caused by inadequate illness management at the onset of infection (Nandhini *et al*., 2022).A significant contributing element to antibiotics' inefficiency against MRSA infection is the acquisition of antibiotic resistance genes through horizontal gene transfer pathways and various other virulence genes have also been associated with increased mortality (Uddin *et al.*, 2021).

The introduction of multiple novel antibiotics, either singly or in combination, has brought hope to individuals affected with MRSA (Wakelin *et al*, 2023). Additionally, researchers are moving away from single-agent treatment and toward immunotherapy, combination treatment and cutting-edge non-antibiotic methods of treating MRSA infections, like bacteriophages, probiotics, phytochemicals, and nanoparticles (Vena *et al*., 2023).

Antibiotic-resistant bacteria are one of the largest hazards to public health, according to the World Health Organization (WHO). Antibiotic-resistant bacteria cause about 700,000 deaths worldwide each year; by 2050, that figure may rise to 10 million (Mizusawa *et al*., 2023).

According to a WHO study, the possibility of antibiotic treatment in which prevalent diseases and minimal infections could be fatal is quite real for the twenty-first century (Burgin *et al*., 2022) Antibiotic-resistant bacterial infections must therefore be managed and treated using innovative, antibiotic-free methods, which must be developed immediately (Noorulamin *et al*., 2022).

Current Antimicrobials Effective Against MRSA Treatment

Tedizolid is a novel medication from the oxazolidinone class that has been recommended for use in the regular 6-day course of treatment for infections of the skin and soft tissues. It works better and has more advantages than linezolid (Nandhini *et al.,* 2022). However, treating gram-positive bacteria with eravacycline is four times more effective than tigecycline (Periferakis *et al.,* 2023).
An aminomethylcycline called omadacycline is more useful for treating acute bacterial skin infections as well as skin structural infections and CAP. Delafloxacin's efficacy was high as compared to that of vancomycin and linezolid in a study conducted in the United States in 2011. Delafloxacin, linezolid, and vancomycin were the three medications that showed the highest rates of cure (Wilcox *et al.*, 2023).

Risk Factors for MRSA Infection in Hospitals

The primary risk factor for the infection of MRSA is patient-to-patient Spread of MRSA. Even though case-control research demonstrate which individuals Similar risk factors are passed on by MRSA infections and other multi resistant bacterial colonies, such as length of hospital stay, and use of antimicrobial agents, personal circumstances. The skin-carrying pathogenic agent *S. aureus*, or any of its antibiotic-resistant forms, spreads quickly through touch, and that hospital dissemination involves cloning, in which only a small amount of clones has been identified globally and typically only one or two clones at a time support this theory (Mizusawa *et al*., 2023).

CHAPTER III

Methodology

This section summarizes the study's objectives, volunteer selection, demographics, and data collection and analysis techniques. Along with the study's validity and reliability, issues related to ethics and practicality were also discussed.

Study Area and Its Criteria

This study was carried out in Northern Cyprus, from October 2023 to December 2023, during which the study period with the following criteria was included in the study:

i. Randomly selected nasal samples from the general population in Northern Cyprus
ii. The volunteers with no signs and symptoms were included

Questionnaire

The bio-data of the volunteers was collected through a questionnaire form that includes their age, geographical location, country of origin, and the indication of the last use of antibiotics.

Ethical Approval

The privacy of the human participants in the current investigation was essential. The study was carried out strictly according to the applicable regulations plus laws and with the greatest regard for ethical considerations. Transparency, confidentiality, privacy, informed permission, and voluntary participation thus became the guiding principles for the design and performance of this study. The project demonstrates that the methodologies and equipment employed were appropriate for this study and the approved by the Near East University Ethics Committee

Media	Ingredients	Origin
HiCrome	Peptone, sodium chloride, sodium pyruvate, chromogenic substance, inhibitor mixture.	Netherlands

Specimen collection

Sterile nasal swabs were used to collect samples from general population living Northern Cyprus. On each tube, the population name and date were marked. Nasal swabs were collected at the sample collection point in a hospital laboratory.

Statistical analysis

The Pearson chi-square was the testing method for the result in this study, with an SPSS version 27 for all statistical analysis. A P-value of 0.005 was considered significant

Media Preparation

HiCrome MRSA agar, blood agar and Muller-Hinton agar preparation.

Blood agar	Heart Muscle, infusion, pancreatic digest of casein, yeast extract, sodium chloride, agar	USA
Mueller-Hinton	Beef extract powder, starch, agar, acid digest of casein	USA

HiCrome MRSA agar was used to culture nasal samples. First weighed HiCrome agar in dried form and mixed it well with the desired amount of distilled water in a flask. Then it was properly sealed with aluminum foil and cotton. HiCrome media was boiled at 100°C for 10 minutes. Then the boiled flask was placed on the bench and let it cool. When the media was cooled, it was poured into sterilized petri dishes. The plates were left aside until the media was solidified. Blood agar and Mueller-Hinton agars used in the study were prepared according to the manufacturer's instructions and were autoclaved before used.

Inoculation

A platinum wire loop of diameter 4mm was used for the inoculation of nasal swabs. The platinum wire loop was sterilized by flame and cooled in air. Inoculation was performed near the flame so that sterile conditions were maintained. Nasal swabs were streaked on solidified HiCrome agar plates and incubated in the incubator at 37°C for 16-24 hours. Specimens collected from the volunteers were transferred to Near East University Microbiology Laboratory within 2 hours of collection.

Macroscopic Examination of culture

After the incubation, the cultures were examined macroscopically. The phenotypic characteristics including colony morphology, pigmentation, and colony

color and size were reported. The microbial colonies with green and blue colors were collected and used for a further test while the rest of the colony were not used.

Preparation of McFarland Standard

Three ml of normal saline was transferred into the test tubes using a micro-pipette and a pure colony from the blood agar was placed into the normal saline tubes. A vortex machine was used to stir the mixture up in the tubes to meet a uniform turbidity and a uniform concentration of the bacterial colony in the test tube. After these procedures, a spectrophotometer was used to measure the turbidity of the tube which was within the range of 0.5-1.2 (McFarland standard).

Cefoxitin Disc Diffusion test

By EUCAST guidelines, a disk diffusion test was conducted to identify MRSA isolates using 30µg of Cefoxitin. Few colonies were taken from blood agar and mixed with 0.9% NaCl solution to prepare a bacterial suspension. Then a volume of bacterial suspension was distributed evenly over the surface of Mueller-Hinton agar by a cotton swap. The density of that suspension was equivalent to 0.5 McFarland standards. Furthermore, 30 µg Cefoxitin disks (ROSCO, Co., Denmark) were placed onto Mueller-Hinton agar plates. As control, NCTC 12493 (mecA-positive *S. aureus*), NCTC 13552 (mecC-positive *S. aureus*), ATCC 25923 (mecA-negative *S. aureus*), and water (negative control) were used.

Plates were incubated at 35ºC for 24-48 hours. The millimeter measurements of the inhibition zone diameters were interpreted under EUCAST guidelines. Methicillin-susceptible (MRSE) strains were defined as having an inhibition zone of >20 mm, whereas strains with an inhibition zone of 14–20 mm were considered methicillin-resistant.

mec A and mec C Detection

For DNA extraction, suspensions of MRSA-suspected strains prepared with 4 McFarland units, were boiled for 10 minutes, and then clarified by centrifugation at 10 000 g for 5 minutes. Isolated DNAs were stored at -30°C for further analysis.

CHAPTER IV

RESULTS

A total of 150 samples were collected through nasal swabs from general population in Northern-Cyprus. Detailed information on their age, gender, origin country, addresses, and a question on their antibiotics usage was also obtained. The distribution of these characteristics is detailed in Table 1 and Figure 1 was also to represent the spatial distributions of country of origin of volunteer's.

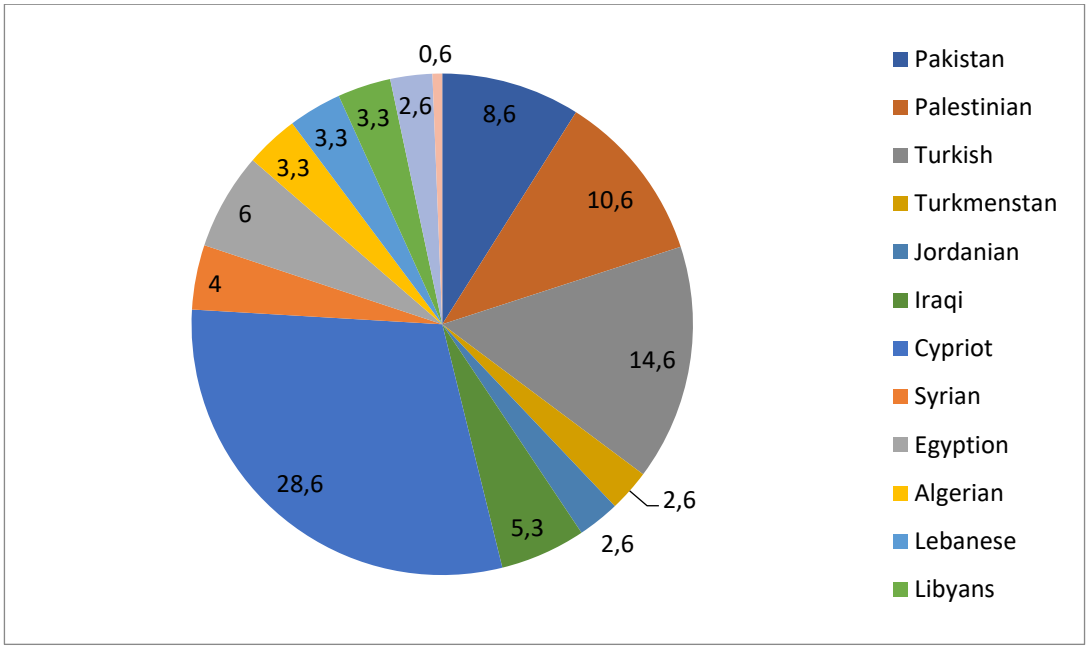
Table 1

Demographic characteristics of the study group

Variable	**Characteristics**	**n(%)**
Age		
	17-26 / Median age(21.5)	73.8
	27-36 /Median age (31.5)	14
	37-46/Median age(41.5)	3.3
	47-56 /Median age(51.5)	0.6
	57-66 /Median age(61.5)	8.6
Region		
	Nicosia	73.3
	Lefke	10
	Kyrenia	6.6
	Magusa	8
Gender		
	Male	49.3
	Female	50.6

Figure 4. 1

The Distribution of the Study Group by Origins



After incubation of inoculated HiCrome agar petri plates for 16-24 hours, the cultures were examined. Twenty two out of 150 samples (14.6%) were reported as no growth which indicates that no colony was reported on the HiCrome agar. Smooth colonies with six different colors were observed with the remaining of 128 samples that showed the presence of MRSA and MRSE according to the manufacturer instructions. The presence of greenish-yellow and green colonies was considered to be MRSA (38/150, 25.4%), while the blue, denim blue was considered to be MRSE (90/150, 60%). Table 4.2, Figure 4.2, Figure 4.3, and Figure 4.4 represents the colony morphologies of the isolated bacteria.

Table 4. 2

Colony Morphology of the Isolated Bacteria On HiCrome Agar

Organism	**Colony characteristics**	**Percentage (n,%)**
MRSA	Green, Greenish yellow, smooth	38,25.4
MRSE	Blue, light blue, denim blue	90,60
No growth	No colony	22,14.6

MRSE: Methicillin Resistance Staphylococcus epidermis

MRSA: Methicillin Resistance Staphylococcus aureus

Figure 4. 2

Blue Colonies on HiCrome Agar That Were Considered as MRSE

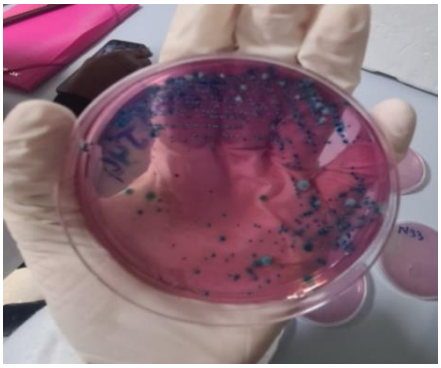


Figure 4. 3

Greenish Yellow Colonies on Hicrome Agar that were Considered MRSA

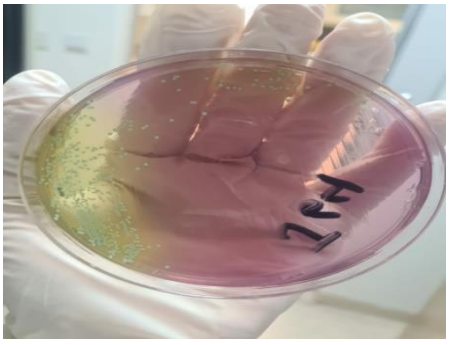


Figure 4. 4

Greenish-yellow colonies on HiCrome Agar that Were Considered MRSA

The suspected MRSA colonies were sub-cultured on blood agar to obtain pure colonies from the blood agar after incubating for 18-24. Different colony morphology was observed having different shapes and colors. Small white opaque with non-hemolytic were observed in 90 samples which were considered to be MRSE while grey, yellowish color with beta-hemolysis was also seen in 38 samples from the blood agar were also considered to be MRSA. Table 4.3 and Figure 4.3 represent the colony morphologies of the isolates

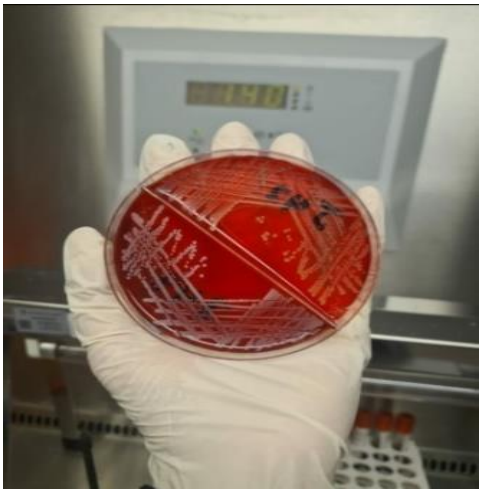
Table 4. 3

Characteristics of the Colony Morphology of the Isolated Bacteria on The Blood Agar

Organism	**Colony characteristic**	**Hemolysis**
MRSA	Smooth large yellow to grey colony	Yes

Figure 4. 5

Macroscopic Examination of Isolated Bacteria on Blood Agar



The Cefoxitin Disc Diffusion technique was used to differentiate between MSSA and MRSA among all the *Staphylococcus* isolates from nasal samples. After the Cefoxitin diffusion test, 9 samples out of the 38 (9/38, 23.6%) were found to be resistant to Cefoxitin and were stored to be confirmed as MRSA. However, 29 out of 38 (29/38, 76.3%) were found to be sensitive to Cefoxitin disk. (Table 4.4, Figure 4.6 and 4.7)

Table 4. 4

Comparison of Two Methods for MRSA Detection

Methods	**Resistance to Cefoxitin(n.%)**	**Sensitive to Cefoxitin(n.%)**
HiCrome positive	9, 23.6	29, 76.3
HiCrome negative	0, 0	90, 60
Total	9	119

Figure 4. 6

Isolates Sensitive to Cefoxitin Disk

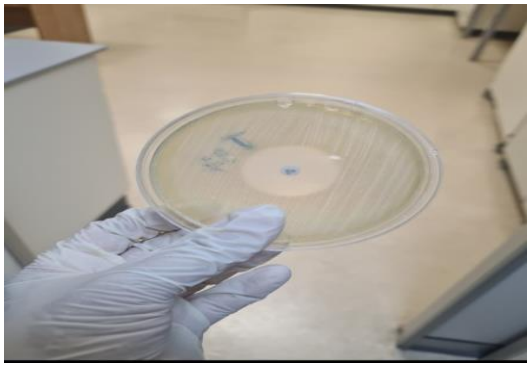
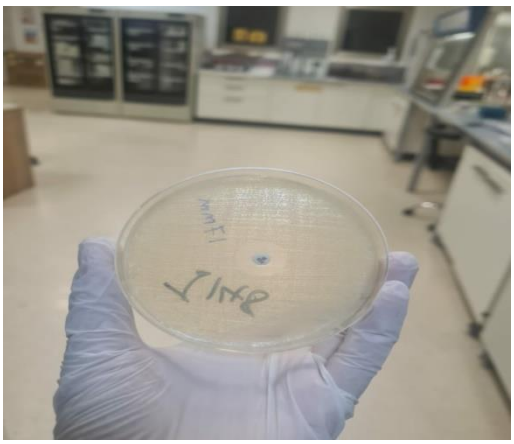


Figure 4. 7

Isolates Resistant to Cefoxitin Disk



The sensitivity of the HiCrome agar was 100% and the specificity was 50%. For the Cefoxitin disk, the sensitivity and specificity were 100%

Table 4. 5

Comparison of MRSA's sensitivity and specificity using HiCrome Agar and Cefoxitin disk

Methods	**Total number of MRSA**	**False Negative**	**False positive**	**Sensitivity(%)**	**Specificity(%)**
HiCrome Agar	38	0	29	100%	50%
Cefoxitin disk	9	0	0	100%	100%

CHAPTER V

DISCUSSION

The acquisition of methicillin resistance in *S. aureus* poses a significant challenge to the management of hospital-acquired infections and numerous community settings. It therefore becomes crucial to screen clinical specimens for MRSA quickly to manage time by using the right medicines and putting isolation measures in place. Thus, assessing a simple, sensitive, accurate, and inexpensive approach is required for early MRSA detection in microbiology labs.

Various techniques were used in this investigation to identify MRSA in this study. A total of 38 samples of *S. aureus* (MRSA, MSSA) were reported from 150 nasal swab samples and MRSA was 9/150 (6%). In this study, we examined two alternative phenotypic approaches for MRSA identification. Total 38 *S. aureus* were isolated from nasal swab samples and were processed for MRSA detection. 9(6%) of these were detected as Methicillin Resistant *S. aureus* (MRSA) through the disk diffusion test with Cefoxitin. HiCrome Agar technique revealed 38 samples to be MRSA. The Cefoxitin disk test has 100% sensitivity and specificity as well with 100% positive and negative predictive value. Other researchers had similarly found 100% sensitivity and specificity with Cefoxitin disc diffusion approaches (Sharma *et al.*, 2017).

However, in the current investigation, 9 out of the 38 MRSA strains identified using the HiCrome agar approach were MRSA. 29 were MSSA with 100% sensitivity and 50% specificity. According to various researches, MRSA Crome agar has a 90% to 100% sensitivity and specificity (Poojary *et al*., 2015). Oxacillin has been substituted by Cefoxitin in the Clinical and Laboratory Standards Institute's disk diffusion tests because that compound is superior to those employing Oxacillin, and the former is confirmed by molecular analysis of MRSA identification by PCR for the mecA gene.

In this investigation, HiCrome agar directly detected 23.6% of the MRSA strains within 24 hours. With a P-value of less than 0.005, sensitivity, specificity, 100%, 100%, 100% & and 50 %, respectively, this was much more significant for

early detection than the Cefoxitin disc diffusion approach. One of the most important steps in spreading the bug's transmission is early discovery.

To measure the efficacy of HiCrome agar method a nasal swab sample was used when the sample had a predisposition to have related commensal flora that could influence isolation but even in situations where there were a lot of contaminated bacteria present, the HiCrome agar approach worked well for early MRSA identification. The outcomes were similar to those of previous researchers' investigations (Anwar *et al*., 2020). This study provided compelling evidence that the nasal carrier may be the origin of community-acquired infections. To stop the spread of such deadly infection, particularly in the high-risk areas of the hospital, MRSA monitoring, good health practices, routine screening, and local treatment of the nasal carriers are crucial. The patient will benefit from early treatment and subsequent prevention of MRSA strain transmission if an early detection approach, such as HiCrome agar, is adopted in place of the laborious multistep conventional method.

A test's accuracy is dependent upon a number of criteria, such as its intended use, the organisms being tested, and the environmental conditions in which it is carried out. The accuracy of the HiCrome agar and Cefoxitin disk test is determined according to their individual applications because they have different uses. The main use of the Cefoxitin disk test is the identification of methicillin-resistant *Staphylococcus aureus* (MRSA). It aids in identifying the resistance of a *Staphylococcus aureus* strain to beta-lactam drugs, including methicillin.

Following conventional protocols, such as selecting the right culture conditions, positioning the disk, and analyzing the data, is essential to the test's accuracy. The Cefoxitin disk test is a trustworthy technique for determining MRSA when carried out appropriately, However The accuracy of HiCrome agar is dependent on its formulation and its capacity to differentiate between various species based on the color changes caused by enzymatic reactions. HiCrome agar is a type of chromogenic agar used for the selective and differential identification of particular microbial species. When used in accordance with the manufacturer's directions, it is generally regarded as effective for the identification of target organisms.

CHAPTER VI

Conclusion and Recommendation

CONCLUSION

The rise in MRSA infections among general population residing in Northern Cyprus who have no known risk factors and who have never interacted with the healthcare system, along with MRSA isolates possessing a distinct genetic component, is a cause for increasing concern. This study showed a low percentage of MRSA carriers among the general population of TRNC (6% of 150 samples collected across the country) because of the low usage of broad-spectrum antibiotics and improved hygiene within healthcare facilities and communities. In addition, considering updated healthcare strategies to successfully stop the spread of microorganisms resistant to antibiotics among the general public.

The most reliable technique for detecting methicillin-resistant *Staphylococcus aureus* in this investigation is Cefoxitin disc diffusion. But the main disadvantage is that it takes a lot of time. Therefore, HiCrome agar approach is a better option for fast identification and rapid screening of MRSA from clinical samples especially in high-risk wards and ICUs as this approach is highly specific and sensitive. This will help with early diagnosis and further prevent the spread of MRSA strain.

Recommendations

The following are the recommendations:

1. Washing your hands regularly with soap and use of alcohol-based sanitizers helps stop the spread of MRSA.
2. Take care of yourself by showering frequently and covering wounds until they heal.
3. To prevent antibiotic resistance, avoid using antibiotics needlessly and finish recommended courses.
4. Isolation to stop the spread of MRSA, and segregate patients who are carrying the infection in medical facilities.

5. Particularly in healthcare settings, give shared surfaces a thorough cleaning and disinfection.
6. Educate carriers and medical professionals about the prevention and transmission of MRSA.
7. It is possible to detect MRSA carriers and put preventative measures in place by conducting routine screenings for carriers, particularly in healthcare facilities.
8. Certain decolonization techniques, such as utilizing particular antiseptic chemicals to lower MRSA, may be used in certain situations.

Limitations of the Study

In the preparation of HiCrome agar in the study, the MeReSa selective supplement (FD229) and Cefoxitin supplement (FD259) weren't added so it affected some of the results on the HiCrome agar.

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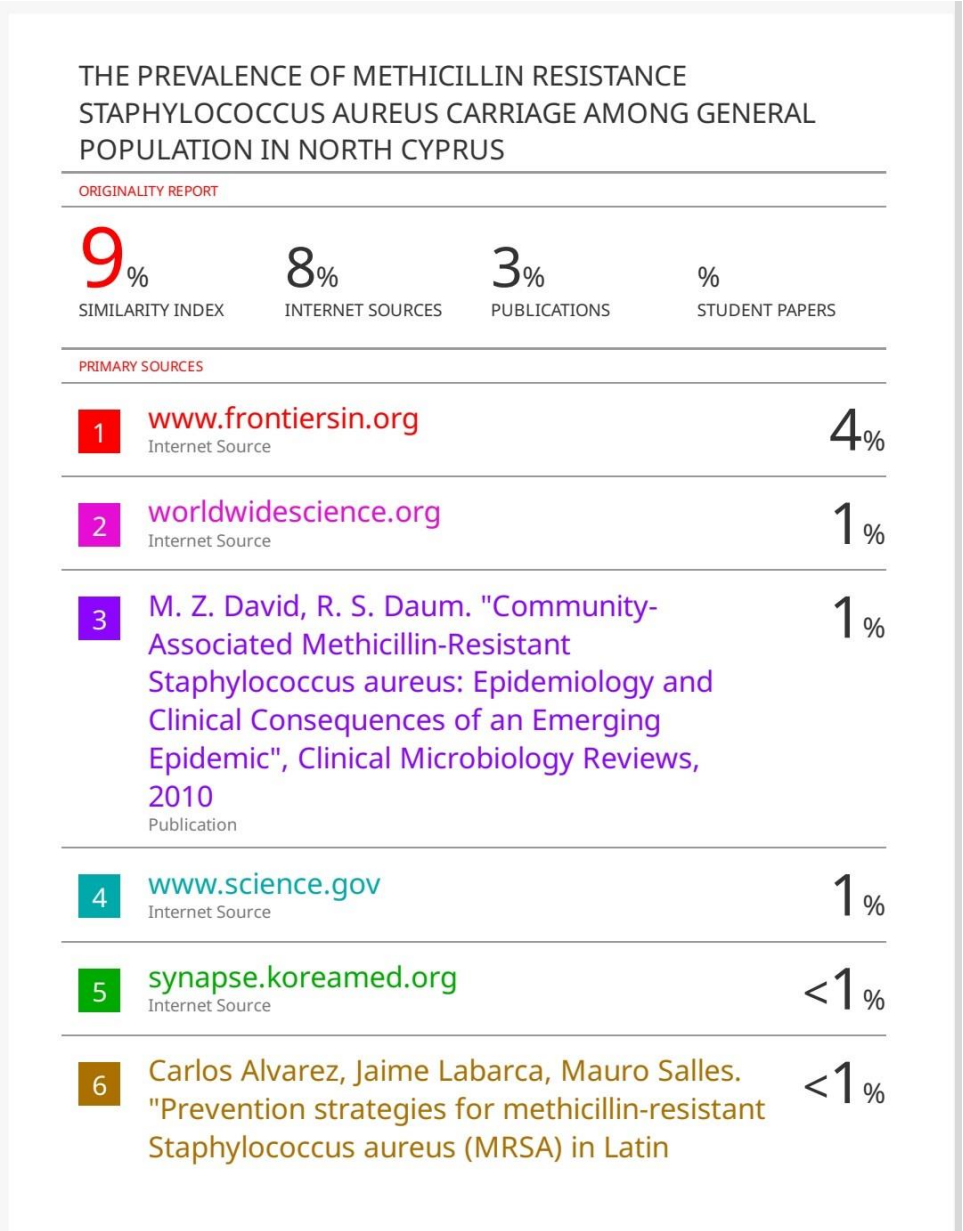
Appendices

Similarity Report



THE PREVALENCE OF METHICILLIN RESISTANCE STAPHYLOCOCCUS AUREUS CARRIAGE AMONG GENERAL POPULATION IN NORTH CYPRUS

ORIGINALITY REPORT

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NEAR EAST UNIVERSITY
SCIENTIFIC RESEARCH ETHICS COMMITTEE

RESEARCH PROJECT EVALUATION REPORT

Meeting date :29.02.2024
Meeting Number :2024/121
Project number :1823

The project entitled **"Investigation of Community-Acquired Antimicrobial Resistance Between People of African Origin Living in TRNC and TRNC Indigenous People"** (Project no: NEU/2024/121-1823), which will be conducted by Assoc. Prof. Dr. Ayşe Arıkan has been reviewed and approved by the Near East University Scientific Research Ethical Committee.

Prof. Dr. Şanda Çalı
Near East University
Head of Scientific Research Ethics Committee

Committee Member	Role	Meeting Attendance *Attended(✓)/Not attended(X)*	Decision *Approved(✓)/Rejected(X)*
1. Prof. Dr. Şanda Çalı	Head	✓	✓
2. Assoc. Prof. Dr. Gulifeiya Abuduxike	Rapporteur	✓	✓
3. Prof. Dr. Tamer Yılmaz	Member	✓	✓
4. Prof. Dr. Şahan Saygı	Member	✓	✓
5. Prof. Dr. İlker Etikan	Member	✓	✓
6. Assoc. Prof. Dr. Mehtap Tınazlı	Member	✓	✓
7. Assoc. Prof. Dr. Dilek Sarpkaya Güder	Member	✓	✓
8. Prof. Dr. Burçin Şanlıdağ	Member	✓	✓

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Nationality: Palestinian

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Contact:00971595872419/+905338899727

Education:

Bachelors in medical laboratory science

Master in medical and clinical Microbiology(2022-2024)Near east university

Experience

Rafedya Hospital:3 months training in specimens collection, interpretation the results of clinical chemistry and in Hematology and immunology.

Al Rahma clinic:2 months same as above

Al Tadamon clinic:8 months same as above

Online courses and Workshops:

Microbiology workshop for one Months

Bacterial identification course for 2 month