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Resistance of Uropathogens at Governmental Hospitals in the Gaza Strip

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Resistance of Uropathogens at Governmental Hospitals in the Gaza Strip

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Dedication

I dedicate my dissertation work to my family and many friends.

A special feeling of gratitude to my loving Mother and sol of my father, My wife, my kids and my niece Asseel whose words of encouragement and push for tenacity ring in my ears.

My sister Rana, and Souls of Reem and Samah and my brothers Hazem and Hatem who have never left my side and are very special.

I also dedicate this dissertation to my all my family and friends who have supported me throughout the process.

I will always appreciate all they have done, especially Ayman El-khozondar for helping me develop my technology skills.

Sameh Alkhodari

Declaration

I certify that this thesis submitted for the degree of master is the result of my own research, except where otherwise acknowledged, and that this thesis or any of its parts has not been submitted for higher degree to any other university or institution

Signed:

Sameh Alkhodari

Date: 20 /12 /2020

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Sameh Alkhodari

Abstract

Misuse and overuse of antimicrobials are considered the main causes of uropathogenic resistance. World Health Organization encouraging countries to implement antimicrobial stewardship programs, for appropriate use of drugs that could minimize drug resistance across time. The overall aim of this study is to determine the occurrence of uropathogens, to explore the pattern of their resistance to antimicrobials and test for difference among gender, age groups, and hospitals. In addition, the study assessed the effect of the implementation of the microbiology standard operating procedure (SOP) and the level of adherence by the laboratories of four governmental hospitals in the Gaza Strip.

A retrospective study (from 1/1/2019 to 31/12/2019) examined 11,890 urine culture records of the Microbiology Department of European, Al-Shifa, Al-Nassr, and Al-Durra Hospitals. All data were tabulated and analyzed. Data analysis was performed using SPSS edition 22. Variables were compared using cross-tabulation the statistical tests of significance were performed; chi-square (X^2) test, independent T-test, one-way ANOVA test, P-value $\leq .05$ was considered statistically significant. Three focus groups, three key informants, seven individual interviews have been conducted and fifteen laboratory technicians responded to a questionnaire. All of them from the microbiology department at the governmental hospitals in the Gaza strip. A semi-structured question the effect and level of adherence to the participants was used. The study was initiated after obtaining a permission from the Helsinki Committee.

The findings showed that *E. coli* was the most common uropathogens in Gaza Strip (59.9%) followed by *Klebsiella* spp. (24.9). The prevalence of UTI in females is higher than males (71%), however, resistance of isolates to antimicrobials is higher in males. In addition, there is general increased resistance of the isolates against tested antibiotics, which limits the empirical treatment options.

Penicillin is no longer suitable for UTI treatment because the microorganism's resistance against this antibiotic group is closed to 90%. Resistance to ampicillin (92.4%), amoxicillin (91.1%), followed by co-trimoxazole (68.2%), cefalexin (64.9%), doxycycline (61.9%), nalidixic acid (53.6%), cefuroxime (53.0%), ceftriaxone (48.9%), ceftazidime (43.1%), ciprofloxacin (36.9%), gentamicin (25.8%). The least resistance was demonstrated against amikacin (3%) and meropenem (8%).

The adherence to the SOP by the staff is high but not perfect and requires follow up by laboratory administration. Furthermore, there is no integration between the physician protocol and laboratory SOP.

In conclusion, the resistance of uropathogens varied from one hospital to another, among gender and among age groups. Factors contributing to the increasing resistance in general and at Al-Shifa Hospital in particular should be investigated in further studies. There is a need for an antimicrobial stewardship program to prevent exacerbation of the problem, and decrease MDR in the community. In addition, SOP needs more follow up and integration with all of the other hospital departments.

Keywords: Uropathogens, Antimicrobial resistance, Urinary tract infection, Gaza strip, Palestine

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Abbreviations

AMR	Antimicrobial resistance
ANOVA	One-Way Analysis of Variance
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
E. coli	*Escherichia coli*
GI	Gastrointestinal
K. pneumoniae	*Klebsiella pneumoniae*
MIC	Minimum Inhibitory Concentration
MoH	Ministry of Health
NGO	Non-Governmental Organization
OECD	Organization for Economic Co-operation and Development
PCBS	Palestinian Central Bureau of Statistics.
PDR	Pan Drug-Resistant
SOP	Standard operating procedure
SPSS	Statistical Package for the Social Sciences
UNRWA	The United Nations Relief and Works Agency for Palestine Refugees in the Near East
USD	United States Dollar
UTI	Urinary tract infection
WHO	World Health Organization
XDR	Extensively Drug-Resistant

Chapter One

Introduction

1.1. Background

Bacterial resistance to antimicrobial is a global critical problem (Holmes et al., 2016). The extent of the problem in low-and middle-income countries is unknown because of the scarcity of data, but high levels of resistance are increasingly being reported worldwide (WHO, Leopold, et al., 2014a, Lestari, 2012). Misuse and overuse of antimicrobials are main causes of antimicrobial resistance (Laxminarayan, et al., 2013, WHO, 2012).

Urinary tract infection is the second most common clinical indication for empirical antimicrobial treatment in primary and secondary care, and urine samples constitute the largest single category of specimens examined in most medical microbiological laboratories (Shill, Huda, Moain, & Karmakar, 2010). Healthcare practitioners regularly have to make decisions about prescription of antimicrobials for UTI. Criteria for the diagnosis of UTI vary greatly, depending on the patient and the context (Shill, Huda, Moain, & Karmakar, 2010).

In Palestine, antimicrobials are poorly regulated and available on the private market without a prescription (Kanapathipillai et al., 2018). As an example; a study in Palestine reports emerging ciprofloxacin resistance among UTI isolates. Increasing resistance against ciprofloxacin demands coordinated monitoring of its activity and rational use of the antimicrobials (El Astal, 2005).

There is high prevalence resistance uropathogens and, therefore, antimicrobial selection should be based on knowledge of the local prevalence of uropathogens and their

antimicrobial sensitivity, rather than empirical treatment (Ayelign et al., 2018). Different microorganisms can cause UTIs; *Escherichia coli* (*E. coli)* which accounts approximately for 75% of isolates it is the most common pathogen isolated from community and hospital acquired UTIs (Jinnah et al., 1996). Other uropathogens such as *Klebsiella* species and *S. saprophyticus* have also been frequently isolated (Ronald, 2002. Lau et al., 2004).

Antimicrobial stewardship, which is designed to rationalize the use of antimicrobials, therefore one of the key actions of the World Health Organization Global Action Plan to contain antimicrobial resistance (Laxminarayan, 2013. WHO, 2012.WHO, 2015) The Palestinian Ministry of Health with the intention of improving surveillance through strengthening the microbiology laboratories, formulated and implemented their own standard operation procedure (SOP). This SOP guides laboratory technicians/ microbiologists in selecting suitable antimicrobial disks for various clinical isolates organism in accordance to guidelines. In this research the antimicrobials resistance profiles of the bacteria from urine cultures in four governmental hospitals were compared and correlated to age, gender, area of living. In addition, the level of adherence to SOP by microbiology laboratories was evaluated.

1.2. Research problem

Antimicrobial resistance is rising to hazardously high levels all over the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases (WHO, 2019).

A growing list of infections such as tuberculosis, pneumonia, septicemias, gonorrhea, and foodborne diseases are becoming more difficult, and sometimes impossible, to treat as antimicrobials become less effective (IBID).

It is clear that the problem is exacerbating day after day and scarce number of studies has been conducted about the bacterial resistance, especially in UTI, and many aspects are still ambiguous. Health care providers are in need of such studies, which determined the antimicrobials bacterial resistance, and compared the resistance levels among different hospitals of Gaza Strip, and to test the effectiveness of the application of the new SOP, and to review matching between guideline and actual use of antimicrobial discs in cultures.

There are threats of new diseases emerging due to the evolution/adaptation of microbes, and the re-emergence of old diseases, due to the development of antimicrobial resistance (Jones et al., 2008). One of factors have contributed to the emergence of infectious disease is irrational antimicrobials usage (Kilpatrick, 2012) (Morse, 1996-a).

There has been an extensive progress in the prevention, control and even elimination of some infectious diseases with improved hygiene and sanitation practices along with the development of antimicrobials and vaccines (Jones et al., 2008). However, they still remain a major public health concern, especially in the developing world, in view of the associated high morbidity and mortality. Moreover, there have been threats of new diseases emerging due to the evolution/adaptation of microbes and the re-emergence of old diseases due to the development of antimicrobial resistance (Jones et al., 2008).

The impact of the emerging and re-emerging diseases has been enormous at socioeconomic and public health levels and it presents a great challenge for the future. Their control requires continuing surveillance, research and training, better diagnostic facilities and remodeled & well-equipped public health system.

The main problem is the increasing of the resistance of uropathogens due to irrational use of antimicrobials which facilitates emerging and re-emerging of communicable diseases that were eradicated before which makes it difficult to be treated by the available

antimicrobials because of developing of the resistance of uropathogens to antimicrobials. On the other side, there is a scarcity of the local researches about this subject. this research, filled the gap of the information about the development of the pattern of the resistance of the uropathogens, to the antimicrobials during a year at four governmental hospitals.

This research helped me as a pharmacist, working at a hospital for rehabilitation, in which the main problem for my patients is UTI, so this research increased my acknowledge about the antimicrobials effect on uropathogens. It will help the MoH hospitals prescribers to modify and redirect their prescription to the effective antimicrobial in UTI according to the findings. Also because of the study covers governmental hospitals and they present service for the community as a whole, this research tried to spare society the risk of increasing the resistance to antimicrobials, the difficulty communicable diseases in addition to emerging and reemerging of the communicable diseases.

Data generated from this research may be prove useful for physicians, medical institutions, community and decision makers. Ultimately, it is a small contribution in the battle against antimicrobial resistance.

1.3. Justification of the study

There is a global interest of empirical use of antimicrobial, abuse of antimicrobial, increasing bacterial resistance, and superbugs. The World Health Organization (WHO) confirms in most of its publications, and committees the importance of these issues. The Palestinian Ministry of Health (MoH) used several approaches to address the high resistance of bacteria to antimicrobial, including workshops, public awareness, prescriber education and the development of the standard operation procedure (SOP), because the high resistance of bacteria to antimicrobial closes the door of many treatment plans, and

thus getting cases worse, and narrowing the field, and decreasing the alternatives, especially in the complicated cases, and sometimes reaching a dead end.

It maybe happens, that prescriber is prescribing antimicrobials empirically; depending on the general instruction for the antimicrobial spectrum, prescriber thinks that he is saving time and giving a hand for improvement faster but, the consequences of this action are very dangerous on all of the community on the long term. Uncontrolled dispensing of antimicrobials, especially during the Great Marsh of Return, injured people especially most of them are youths increases the problem consequences.

This study explained the extent of antimicrobial resistance in urinary tract infected patient at four main hospitals in Gaza Strip, and determine differences among these hospitals. This may help prescribers to determine the proper antimicrobial. In addition, this study determined if the intervention (represented by the introduction and application of microbiology (SOP) is effective by assessing the extent of adherence of laboratory technician to the standards. Palestine like other developing countries, faces irrational antimicrobial use problem due to prescribing patterns, and it is important for the policy makers and design makers to do some important points that are recommended from WHO to control the antimicrobial resistance dilemma, that are Strengthen national multisectoral coordination for the containment of antimicrobial resistance, Strengthen national surveillance of antimicrobial resistance, Promote national strategies for the rational use of antimicrobials and strengthen national surveillance of antimicrobial consumption, Strengthen infection control and surveillance of antimicrobial resistance in health care settings, Prevent and control the development and spread of antimicrobial resistance in the food chain, Promote innovation and research on new drugs and technology, Improve awareness, patient safety and partnership. The researcher hopes that the result of the

research may help in paving the way to organizing the prescribing and dispensing of antimicrobials in UTI.

1.4. Goal of the study

This study is to assess the current status of the antimicrobial resistance of uropathogens and to compare the level of bacterial resistance to antimicrobial among four governmental hospitals. In addition, the study aims at evaluating the (SOP) intervention in the Gaza Strip and to determine the adherence of laboratory technicians to the SOP standards, to obtain better antimicrobial prescription.

1.5. Objectives

- To identify the types of bacteria, and the nature of their resistance to the in-use antimicrobials in urine cultures in four governmental hospital.
- To compare urinary bacterial resistance to antimicrobial among the four governmental hospitals and sites.
- To compare between pre- and post-application of ministry of health SOP.
- To evaluate the extent of adherence of laboratories involved in the study to the recommended guidelines/SOP in urine cultures.
- To develop recommendations for efficient and effective use of antimicrobials by medical team.

1.6. Research questions

1. What are types of bacteria that present in UTI cultures in the four governmental hospitals?
2. What is the resistance percentage of uropathogens for antimicrobial at the four governmental Hospital?

3.Is there a difference in resistance of the uropathogens for the same antimicrobial at different hospitals?

4.Is there a difference in resistance of the uropathogens for the same antimicrobial between adults and children?

5.Is there a difference in resistance of the uropathogens for the same antimicrobial between male and female?

6.What are the prevalent causes of UTI at governmental hospitals?

7.Is the SOP an effective process?

8.Are the laboratory technicians adhering to the SOP in urine bacterial susceptibility/resistance test for antimicrobials?

1.7. Context of the study

1.7.1. Political context

Palestine is considered a small area of land; it has been attacked by many countries and empires for many centuries ago.

Since ever, Palestine has been an important country for invaders, the area is 27027 Km^2. After Nakba in 1947, about 77% of land was occupied and this led to two divided areas Gaza Strip and West Bank with 365 km_2 with coastline of 40 km and 5655 km_2 respectively (Courbage, Abuhamad & Zagha, 2016). The Gaza Strip is a small enclave that hosts a huge number of populations who are facing many crises includes lack of electricity, close the cross boarders, high prevalence of unemployment, and poor economic status for many families. Moreover, in the past ten years, Gaza Strip was exposed to three aggressions, the last one led to killing of 2131 Palestinian and 108000 people became homeless (Courbage, Abu Hamad, & Zagha, 2016). In addition to the Great Marsh of Return and all of its consequences of injuries, infections and treatment by antimicrobials.

All these aggressions may have increased communicable diseases and infection process, which also lead to increase in antimicrobials use.

Unfortunately, use of antimicrobials in Gaza Strip is uncontrolled, especially the empirical antimicrobial dispensing that is leading for sure to antimicrobial resistance and producing superbugs.

1.7.2. Demographic context

The estimated midyear of Gaza Strip was 1.99 million of which 1.01 million males and 980 thousand females (PCBS, 2019). The estimated percentage in rural area was 16.6% and the percentage of population in urban area was 73.9%, while the remaining estimation percentage for those who live in the camp with 9.5% (PCBS, 2016).

The expected population in 2050 in the Gaza Strip is 4.8 Million, exceeding the expected population in West Bank 4.7 Million (Courbage, Abu Hamad, & Zagha, 2016). In the Gaza Strip, the population density is very high with 5203 persons per one km_2 (PCRS, 2018). This huge density might have played a rule in spreading highly resistant bacteria among people. children are more vulnerable to infection. About 50% of the population in Gaza Strip are below the age of 18.

1.7.3. Economic context

The economic status in the Gaza Strip is characterized as poor and low income, most of families has limited resources, unemployment rates in Gaza Strip was 48.2% (PCBS, 2018) higher than 2016, which was 40% (UNRWA, 2016) while for youth, the percentage of unemployment is 60% (UNFPA, 2017).

Furthermore, the poverty rate in the Gaza Strip was 37.6% much higher than West Bank 21.3% (PCBS, 2017), This percentage was slightly decreased from 38.8% in 2011 (PCBS, 2017). Adding to that, this state of poverty rate differs from area to area; for instance, in

the Gaza Strip, Khan Younis possessed the highest rate 45.9%, while north Gaza was the lowest rate in poverty with 28.2% (PCBS, 2017). This reflects the poor economic situation the Gaza Strip is facing. Also, 67.1% of the population who are living in the Gaza Strip are under the poverty line, 21.1% of them are living under the extreme poverty line (Courbage, Abu Hamad & Zagha, 2016).

All these conditions may affect the process of prescribing medicine, because the patient cannot afford physician consultation fees, alternatively, they obtain free consultations from the private pharmacies and buy antimicrobials without prescription, because there are no policies/laws that prevent pharmacist from doing this action, which may be the main reason for antimicrobial overuse and misuse and has consequences on the community.

1.7.4. Health context

There are four major health care providers operating in the Palestinian territories, MoH, UNRWA, NGOs and the private sector. The major providers of primary care services are the MoH and UNRWA. The major providers of secondary services are the MoH and NGOs (Core group on health, 2001).

In Palestine, there are 80 Hospitals, 50 in west bank and 30 in Gaza Strip, there are5939 beds 3502 in west bank and 2437 in Gaza Strip, also there are 1.3 Beds for every 1000 inhabitant (PCBS, 2014). The secondary health care hospitals in Gaza Strip are 14 hospitals with 2313 beds serving 1,899,291 people in five different governorates. This study was conducted on four governmental hospitals:

Al-Shifa Hospital: is considered to be the largest medical health institution in the Gaza Strip. It includes three specialized hospitals, which are the Surgical Hospital, the intentional medicine Hospital, and the Gynecological and Obstetric Hospital, with a total

clinical capacity of 619 beds. It is located in the central western region of Gaza City, and serves the coverage area of the Gaza Governorate, and the Gaza Strip in general.

Al-Nasser Pediatric Hospital: serves the population of Gaza Governorate, the clinical capacity is 132 beds.

Al-Dorra Pediatric Hospital: the total capacity is 91 beds provides pediatric services in the north and east of Gaza Governorate.

European Gaza Hospital: Serves residents of the southern governorates and has a clinical capacity of 246 bed

The chosen hospitals are distributed to cover large area in the Gaza Strip. Al-Shifa hospital is central in Gaza city and cover most of the north area and the middle governorate. The European Gaza hospital is also central hospital between Rafah and Khan Younes and serves a large number of people in the south of Gaza Strip. In addition to the pediatric department that is presents in EGH that is posing service to children that is conducting laboratory culture tests like Al-Nasser Pediatric Hospital and Al-Dorra Pediatric Hospital those are both for children either, one in the east and other in the west of Gaza city. Thus, the comparison is representative of the research population.

According to Palestinian Health Information Center in 2016; the average direct cost per laboratory examination was 2.7 NIS, the total no of microbiology tests in the intermediate governmental laboratories are 84,673 microbiology laboratory tests. The item of medicines and medical consumables amounted is 16% of the item of capital expenditures and other operating are the smallest percentage which amounted to 7% of the total current budget (IBID).

Most countries face large increment in expenditures on pharmaceuticals. Expenditures on drugs account for between 7% and 22% of spending on healthcare in Organization for Economic Co-operation and Development (OECD) countries (Aaserud, Dahlgren, Kösters, et.al., 2006). There is also irrational use of drugs represented by misuse, overuse, and underuse of appropriate drugs which can lead to raising resistance to antimicrobials and other health hazards. The Palestinian per capita health expenditure is higher than regional countries (WHO, 2006). Approximately 25% of MoH budget expensed on drugs, medical supplies and vaccines, in 2003 estimated 27% of MoH budget used for this purpose (15.5West Bank and 11.5 Gaza Strip), of these 18% for hospital and 9% for Primary Health Care (Abed, 2007).

In comparison with neighboring countries at the same level of economic situation, consumption of drugs in the West Bank and Gaza Strip is very high (Obeidallah, Mahariq, Barzeq, & Zemli, 2000). Absence of appropriate drugs policy, and inadequate source for drugs information, led strong patient demand and over prescription (Obeidallah, Mahariq, Barzeq, & Zemli, 2000). Over use of Antimicrobials in governmental primary health care in Gaza Strip, where it represents 33% from total Primary Health Care drugs expenditure in 2005 (MoH, 2006).

The results of drugs situation analysis among UNRWA agency widely indicate that Gaza has the highest expenditure on medical supplies per outpatient, 1.5 United States Dollar (USD) than other regions. The average expenditure on medical supplies per registered refugee in Gaza was 4.5 USD, which also higher than other regions Agency wide (UNRWA, 2004).

Note :75% from medical supply are drugs while 25% include Lab, Dental and vaccine

1.8. Definitions

Susceptible The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the recommended dosage is used for the site of infection (Clinical and Laboratory Standards Institute (CLSI) definition).

Resistant The "resistant" category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules, and/or that demonstrate zone diameters that fall in the range where specific microbial resistance mechanisms (e.g., beta-lactamases) are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies (CLSI definition).

Intermediate 'The "intermediate" category includes isolates with antimicrobial Minimum Inhibitory Concentration (MICs) that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates.

The intermediate category implies clinical efficacy in body sites, where the drugs are physiologically concentrated (e.g., quinolones and beta-lactams in urine) or when a higher-than-normal dosage of a drug can be used (e.g., beta lactams).

This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins (CLSI definition).

A superbug: Is a microorganism that's resistant to commonly used antimicrobials – but not all superbugs are equal. The number of different antimicrobials to which it can be resistant determines the degree of the superbug. Some are resistant to one or two, but others can be resistant to multiple drugs. So, if a bug is resistant to every available antimicrobial, it would be the superbug of all superbugs (WHO definition).

Antimicrobial: An agent or substance derived from any source (microorganisms, plants, animals, synthetic or semi-synthetic) that acts against any type of microorganism, such as bacteria (antibacterial), mycobacteria (anti-mycobacterial), fungi (antifungal), parasite (anti-parasitic) and viruses (antiviral). All antibiotics are antimicrobials, but not all antimicrobials are antibiotics (WHO definition).

Antimicrobial resistance (AMR): Microorganisms such as bacteria, fungi, viruses and parasites change when exposed to antimicrobial drugs such as antibiotics (= antibacterial), antifungals, antivirals, antimalarials and anthelmintics. As a result, the medicines become ineffective (WHO definition).

Antimicrobial stewardship (AMS): A coherent set of actions which promote the responsible use of antimicrobials. This definition can be applied to actions at the individual level as well as the national and global level, and across human health, animal health and the environment (WHO definition).

Community-acquired infection: An infection acquired in the community, outside of a health-care setting (WHO definition).

Days of therapy: The number of days a patient receives an antibiotic independent of dose (WHO definition).

Defined daily dose: Assumed average maintenance dose per day for a medicine used for its main indication in adults as established by the WHO Collaborating Centre for Drug Statistics and Methodology (WHO definition).

Empirical antibiotic treatment: Initial antibiotic treatment targeted at the most probable causative microorganism. Recommendations should be based on local susceptibility data,

available scientific evidence or expert opinion, when evidence is lacking (WHO definition).

Health-care-associated infection (also referred to as "nosocomial" or "hospital infection"): An infection occurring in a patient during care in a hospital or other health-care facility, which was not present or incubating at the time of admission. Health-care associated infections can also appear after discharge. They represent the most frequent adverse event associated with patient care (WHO definition).

Multidrug-resistant bacteria: Bacteria that are resistant to at least one agent in three or more antibiotic categories. Extensively drug-resistant (XDR) is non-susceptibility to at least one agent in all but two or fewer antibiotic categories (i.e., bacterial isolates remain susceptible to only one or two categories), and pan drug-resistant (PDR) is non-susceptibility to all agents in all antibiotic categories (WHO definition).

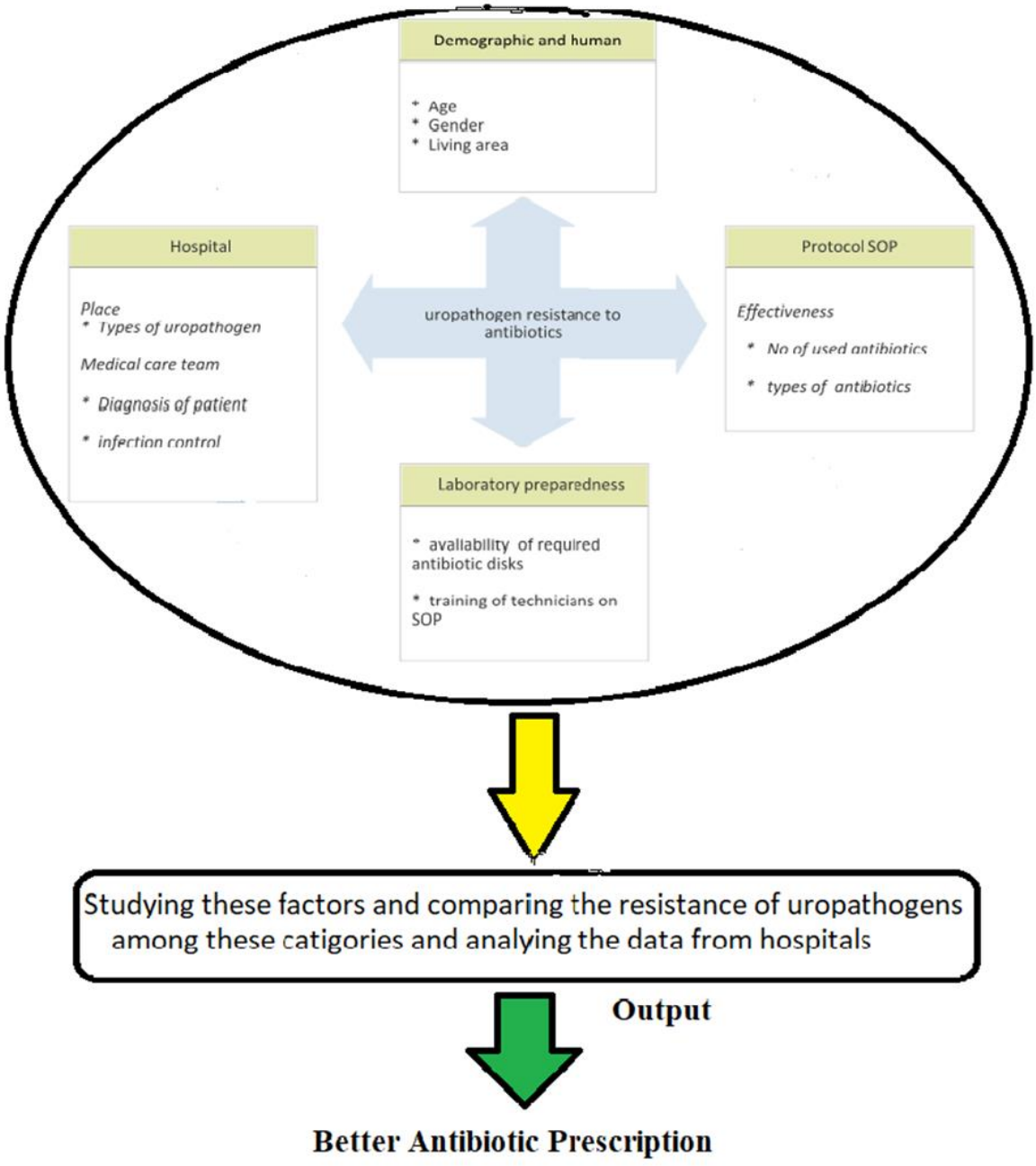
Adherence: Sticking to SOP instructions by using the proper antibiotic disk during testing isolate susceptibility resistance test.

Violation: Breaking SOP instructions by using the proper antibiotic disk during testing isolate susceptibility resistance test.

Chapter Two

Literature Review

2.1. Conceptual frame



Conceptual frame

2.1.1. Uropathogens resistance to antimicrobial

The resistance level of bacteria to antimicrobial depends on many factors, that are affecting directly on the uropathogen susceptibility to antimicrobial so it is important to take care during prescribing antimicrobials to get better results and these factors are as the following

2.1.2. Demographic and human:

According to many studies age, gender, and living area are affecting the resistance susceptibility of uropathogens to antimicrobial so the comparison in this research put these variables into account to obtain good recommendation for prescriber during the empirical prescription.

2.1.3. Hospital:

Every place has its own pathogens and it is a distinctive issue for it and antimicrobials may be effective in a hospital and in effective in another, also medical care team have their effect which can be helpful or sometime harmful that is completely related to good diagnosis and infection control.

2.1.4. Protocol:

Availability of protocol is a very important matter that is controlling the procedure which guarantees the unity of work that makes technician avoids mistakes, and makes him follow the procedure (SOP) that is approved by expertise.

2.1.5. Laboratory preparedness :

The availability of the logistics and good training for the teamwork is the main component of the whole process of controlling the resistance of uropathogen to antimicrobial.

2.2. Uropathogens types and antimicrobial used

Most studies show higher percentage of patients are infected with bacterial pathogens. *E. coli* is the most prevalent organisms causing UTI. *E. coli* as a commonest cause of UTI, it may be due to that this bacterium is considered as a normal flora in intestinal tract and present in high numbers thus may be this bacterial contaminates the urinary tract as the near of region of the body. Most organisms that cause UTI, in most of studies, are belonging to the Gram-negative bacteria (Al-Jebouri, 2006), (Al-Rawi.1998).

There is a number of studies on UTI showed a high elevation in antimicrobial resistance of pathogens isolated from the Iraqi patients compared to previous years (Collee et al., 1996), this might be due to misuse of antimicrobial, usage of antimicrobial from unknown origin. Furthermore, *E. coli*, *Proteus Mirabilis, Pseudomonas aeruginosa*, *Staphylococcus aureus, Klebsiella pneumoniae (K. pneumonia)* and *Serratia marcescens* are still highly susceptible to amikacin and ciprofloxacin. The most common UTI pathogens are highly resistant to antimicrobials emphasize the need for Judicious use of antimicrobials.

Many studies confirm that, *E. coli* remain the most prominent uropathogens which was isolated in 60.29% of the cultures. This is consistent with other studies in many countries is slightly higher. Among the other frequently isolated bacterial uropathogens, the most common were *Pseudomonas* species (8.68%), *Proteus* species (7.79%), *Staphylococcus aureus* (7.35%) and *Klebsiella species* (5.88%) in North East of Ethiopia (Abejew, 2014). This is similar when compared with other studies in different places over the world. These studies have showed that approximately a quarter of *E. coli* isolates were resistant to Amoxicillin, Ampicillin.

Other studies done in Addis Ababa (Assefa et al., 2008) and in Iran (Farajnia et al., 2009). *E. coli* is the major etiological agent in causing UTI, which accounts for up to 90% of

cases. The most frequent uropathogens were Gram negatives which made up 80.9% of all the isolates. *E. coli* is by far the most common bacteria isolated from urine samples in both outpatients and inpatients of both sexes, and this finding is in agreement with others finding too (Farajnia et al., 2009; Tessema, 2007; Rakaa et al., 2004; Dromigny, 2002). The second reported isolates were Staphylococcus species according to some studies (Assefa et al., 2008; Tessema, 2007; Dromigny, 2002), but some other studies it was *K. pneumoniae* which is in agreement of (Khameneh, & Afshar, 2009).

2.3. Gender and uropathogen resistance difference to antimicrobials

The most common UTIs occur mainly in women and affect the bladder and urethra, the prevalence of UTI is higher among females than male patients (in a ratio of 2:1), Woman are more prone to have UTI than men this may be because in female, the urethra is much shorter and closer to the anus than in males, and they lack the bacteriostatic properties of prostatic secretions (Collee et al., 1996).

Another study from Ethiopia, out-off 680 cultures at least one bacterial species was isolated. The majority 528 (77.65%) were from females, and 372 (54.71%) from patients of 16-35 years old (Asrat & Agalu, 2014). This supports the idea women are more prone to UTIs (Dipiro et al., 2011; Fauci et al., 2008; Griebling, 2007).

Findings of another study from Afghanistan, when sensitivity to different antimicrobials was compared, Imipenem, Meropenem and Tazocin were found effective against the bacterial isolates from both sexes. It is surprising that all the antimicrobials, except amikacin, showed more resistance in male patients than females. Nitrofurantoin showed about two folds resistance in males than females, while Trimethoprim, cotrimoxazole and ceftazidime showed 11% more resistance in males than females. Ceftriaxone, ciprofloxacin, ampicillin and co-amoxiclav showed 13%, 14%, 16% and 20 % more resistance in males as compared to females, respectively (Bashir et al., 2008).

2.4. Age and uropathogens resistance difference to antimicrobials

Likewise, UTIs were more common among women of reproductive age groups (16-35 years) which agrees with earlier studies in that country and others like Nigeria, India and Kuwait (Griebling, 2007).

When data were classified into different age and gender groups, it appeared that cases of urinary tract infections (UTIs) were more in boys than girls of less than ten years of age. For the age group 20+ the females showed more than double the % of UTIs cases in males. For the next age group (30+) the situation appeared inverse to the preceding age group. Then for the age groups 40+ and 60+ females had 6.64% and 6.73% higher prevalence of the infection respectively than the corresponding male groups. However, for age group 50+ gender wise difference was not prominent. For 70+ age group cases for males appeared double than the females (Mohammed et al., 2007) and they identified sexually active and/or probably pregnant females in this age group are at high risk for UTI.

E. coli was the most prevalent community-acquired uropathogen. Nevertheless, initial empiric antimicrobial treatment of UTI should consider the significant prevalence of other agents different from *E. coli* in infants < 3 months, the high prevalence of *Staphylococcus saprophyticus* in patients > 10 years and *Proteus mirabilis* in males (Lo et al., 2013).

The isolates from below 40 years male patients and age groups 50+ and 70+ showed almost complete resistance to ciprofloxacin, while it was effective in half of male patients in age groups 40+ and 60 + (Bashir et al., 2008). Amikacin experienced little resistance in age groups 20+(16.66 %), 40+ (8.33%), 50+ (10%) and 70+ (16.66%), while for other age groups it was completely effective. Different trends in resistance for the different age groups are shown in this study (Bashir et al., 2008).

The susceptibility of uropathogenic bacteria to antimicrobials is known to change over time and varies among different countries (Sharef, 2015).

2.5. Area of living and hospital referred

Area of living is an important factor that influence resistance of microorganism to antimicrobials, three studies in Ethiopia showed that the prevalence of isolated bacteria in 680 cultures of a specific place of a country were higher, compared with similar studies in the same country (Beyene; Jombo, 2011; ECDPC, 2010). This might be due to data were collected from culture results of patients referred for diagnostic purpose, which has selected for infected cases with gram-negatives 598 (87.94%) bacteria, which were most commonly isolated. Prevalence differs with studies in other parts of the country (Beyene & Tsegaye 2011; Assefa et al., 2008). (Alemu et al., 2012) and other countries like Kuwait, Nigeria and Tanzania (Nasr et al., 2019; Kolawole & Al Benwan, et al., 2010;). This might be due to geographical and/or methodological differences as well large site coverage, difference in source of data, laboratory versus hospitals, from other studies done in Ethiopia or other countries.

2.6. Hospital, Diagnosis and Medical care team

2.6.1. Causes of urinary tract infection:

UTI typically occur when bacteria enter the urinary tract through the urethra and begin to multiply in the bladder. Although the urinary system is designed to keep out such microscopic invaders, these defenses sometimes fail. When that happens, bacteria may take hold and grow into a full-blown infection in the urinary tract.

- **Cystitis** is usually caused by *E. coli*, a type of bacteria commonly found in the gastrointestinal (GI) tract. However, sometimes other bacteria are responsible.

Sexual intercourse may lead to cystitis, but you don't have to be sexually active to develop it. All women are at risk of cystitis because of their anatomy — specifically, the short distance from the urethra to the anus and the urethral opening to the bladder.

- **Urethritis** occurs when GI bacteria spread from the anus to the urethra. Also, because the female urethra is close to the vagina, sexually transmitted infections, such as herpes, gonorrhea, chlamydia and mycoplasma, can cause urethritis.

2.6.2. Risk factors:

UTI are common in women, and many women experience more than one infection during their lifetimes. Risk factors specific to women for UTIs include female anatomy; a woman has a shorter urethra than a man does, which shortens the distance that bacteria must travel to reach the bladder, also sexually active women tend to have more UTIs than do women who aren't sexually active. Having a new sexual partner also increases risk, in addition to certain types of birth control; women who use diaphragms for birth control may be at higher risk, as well as women who use spermicidal agents, after menopause, a decline in circulating estrogen causes changes in the urinary tract that make patient more vulnerable to infection.

Other risk factors like babies born with urinary tract abnormalities that don't allow urine to leave the body normally or cause urine to back up in the urethra have an increased risk of UTIs, kidney stones or an enlarged prostate can trap urine in the bladder and increase the risk of UTIs. A suppressed immune system**.** Diabetes and other diseases that impair the immune system — the body's defense against germs — can increase the risk of UTIs, People who can't urinate on their own and use a tube (catheter) to urinate have an increased risk of UTIs. This may include people who are hospitalized, people with neurological

problems that make it difficult to control their ability to urinate and people who are paralyzed, urinary surgery or an exam of urinary tract that involves medical instruments can both increase risk of developing a UTI (NCH Health Care System USA, 2020).

2.7. Antimicrobial stewardship

The main goals are to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance (Dellit, et al., 2007; Fishman, 2006).

Antimicrobial stewardship is defined as interventions to improve the appropriate use of antimicrobials through promotion of optimal agent selection, dosing, duration and route of administration (Van Schooneveld, 2011), with minimal toxicity to the patient and minimal impact on subsequent resistance. Good antimicrobial stewardship is akin to motherhood and apple pie (Gerding, 2001).

It has a multifaceted approach (including policies, guidelines, surveillance, prevalence reports, education and audit of practice) that healthcare organizations have adopted to optimize prescribing (Charani, Cooke, & Holmes, 2010). Resistance can be talked by dwindling number of antimicrobial agents, and the suboptimal use of antimicrobials in clinical practice (Van Schooneveld, 2011). Reasonability refers to how the judicious use of antimicrobials can maximize both their current effects and the chances of their being available for future generations (Mendelson, 2017)

2.8. Protocol and laboratory preparedness:

According to the SOP of the MoH there are some pints should be taken in to account during conducting the urine culture test: -

Purpose & Definition: An etiological diagnosis of bacterial urinary tract infection by quantitative cultivation of the urine with identification and susceptibility test of the isolated bacteria(s).

Responsibilities:

- Microbiology department personnel are required to be knowledgeable of this procedure.
- New employees are trained and assessed for competence before they can handle patient sample.
- The head of the department must resolve any problem with the process and difficulties in using this SOP.

Specimen requirements: Urine (Midstream urine), suprapubic aspiration, catheterized urine.

Specimen collection:

1. Give the patient sterile container
2. Collect the first morning Midstream urine into sterile container and pass excess into toilet.
3. Clean –catch urine specimen from infant and children: Give the child water or other liquid to drink, Clean the external genitalia
4. Sample must be transported to the laboratory immediately. If it is not possible urine should be refrigerated.

Criteria of specimen rejection

1. Un-refrigerated specimen older than 2 hours may be subject to overgrowth and may not yield valid results.
2. Unlabeled specimen; mislabeled specimen.
3. Patient on antimicrobial therapy.

Equipment & Items required:

1. Disposable 1 µ l sterile loop
2. Blood, and MacConkey agar.

Procedure

1. Mix the sample to re-suspend microorganism present.
2. Dip 1 µ l calibrated loop in vertical position in the urine and remove the loop and use the collected fluid to inoculate blood agar plate that is used for urine plate count.
3. Take another loop to streak MacConkey agar.
4. Incubate the inoculated plates for 24 hrs. at 35 – 37 C.

Interpretation of urine results:

1. Count the number of pathogens using correction factor to obtain the number of colonies forming unit Per ml (1000 if 1 µ loop is used, 100 if 10µ loop is used).
2. No bacterial growth reported negative culture
3. No of organism > 10.000 CFU/ml record name of bacteria and susceptibility test.
4. If the sample catheter or suprapubic aspiration and count of bacteria > 3 X 10^3 CFU/ml recorded name of bacteria and susceptibility test.

2.9. Benefits of the Adherence to the SOP instructions:

A study in ermany aimed to assess the impact of SOP adapted to the local resistance rates in the initial empirical treatment for pneumonia on duration of first pneumonia episode, duration of mechanical ventilation, and length of ICU stay. The study concluded that Adherence to standard operating procedure is associated with a shorter duration of treatment of first pneumonia episode, a shorter duration of mechanical ventilation, and a

shorter ICU stay (Nachtigall, I, 2009). Another study in USA concluded that adherence to SOPs based on evidence-based medicine that consider local resistance rates for antibiotic treatment in elderly ICU patients is associated with a lower mortality rate. (Nachtigall, I., 2008)

2.10. Tables from the SOP show the proper antibiotics for specific isolates

In the following section, three tables from the SOP are presented.

Table 2.1 Recommended antibiotics for *Streptococcus pneumonia* in SOP

Microbiology Standard Operating Procedure (SOP)

وزارة الصحة – الإدارة العامة للمستشفيات – دائرة المختبرات وبنوك دم المستشفيات

Streptococcus Pneumonia

Antimicrobial Agent	Adult	Pediatric	Pregnant Woman
Penicillin G	√	√	√
Cefepime	√	√	√
Erythromycin (not used for urine)	√	√	√
Trimethoprim Sulfamethoxazole	√	√	X
Ceftriaxone, or Cefotaxime	√	√	√
Clindamycin	√	√	√
Vancomycin	√	√	√
Doxycycline	√	X	X
Levofloxacin	√	√	√
Clavulanic acid + Amoxicillin	√	√	√
Cefuroxime	√	√	√
Chloramphenicol	√	X	X
*Meropenem	√	√	√

*لمرضى العناية يضاف لفحص الحساسية من المرة الأولى

*لمرضى الأقسام المختلفة في حال ظهرت الحساسية في المرة الأولى (البكتيريا مقاومة لجميع المضادات الحيوية) يتم عمل فحص حساسية آخر لهذه المضادات

- ✓ **: Should be used**
- × **: Should not be used**

Table 2.2 Recommended antibiotics for non-*Enterobacteriaceae* in SOP

Non *Enterobacteriaceae* include *Pseudomonas app*. And other non-*Fastidious,* glucose non fermenting, gram negative *bacilli*, but exclude *P. aeruginosa, Acinetobacter*

spp. Because there are separate lists of suggested drugs to test and report for them.

Antimicrobial Agent	Adult	Pediatric	Pregnant Woman
Ceftazidime	√	√	√
Cefepime	√	√	√
Gentamicin	√	√	**X**
Amikacin	√	√	**X**
Ciprofloxacin or Levofloxacin	√	√	**X**
Trimethoprim sulfamethoxazole	√	√	**X**
Cefotaxime or Ceftriaxone	√	√	√
Chloramphenicol	√	**X**	**X**
Doxycycline	√	**X**	**X**
*Piperacillin + Tazobactam	√	√	√
*Meropenem	√	√	√

*لمرضى العناية يضاف لفحص الحساسية من المرة الأولى

*لمرضى الأقسام المختلفة في حال ظهرت الحساسية في المرة الأولى (البكتيريا مقاومة لجميع المضادات الحيوية) يتم عمل فحص حساسية آخر لهذه المضادات

- ✓ **: Should be used**
- × **: Should not be used**

Table 2.3 Recommended antibiotics for *Enterobacteriaceae* in SOP

وزارة الصحة ـ الإدارة العامة للمستشفيات ـ دائرة المختبرات وبنوك دم المستشفيات

Citrobacter freundii, Enterobacter, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Morganella morganii, Proteus mirabilis, Serratia marcescens

Antimicrobial Agent	**Adult**	**Pediatric**	**Pregnant Woman**
Gentamicin	√	√	**X**
Cefotaxime or Ceftriaxone	√	√	√
Cefazolin	√	√	√
Cefepime	√	√	√
Cefuroxime	√	√	√
Ciprofloxacin or Levofloxacin	√	√	√
Trimethoprim Sulfamethoxazole,	√	√	**X**
Amikacin	√	√	**X**
Ceftazidime	√	√	√
Chloramphenicol	√	**X**	**X**
Doxycycline	√	**X**	**X**
*Piperacillin + Tazobactam	√	√	√
*Meropenem	√	√	√
U: Additional agent for urine			
Nitrofurantoin	√	**X**	√
Nalidixic acid	√	√	√

لمرضى العناية يضاف لفحص الحساسية من المرة الأولى

*لمرضى الأقسام المختلفة في حال ظهرت الحساسية في المرة الأولى (البكتيريا مقاومة لجميع المضادات الحيوية) يتم عمل فحص حساسية آخر لهذه المضادات

WARNING: For Salmonella spp. and Shigella spp., 1st- and 2nd-generation Cephalosporins and Cephamycin may appear active in vitro, but are not effective clinically and should not be reported as susceptible.

- ✓ **: Should be used**
- × **: Should not be used**

Chapter Three

Methodology

This chapter presents the study methodology. The chapter includes study design, type of study, sample, study population, and ethical consideration. In addition, it presents the instruments, which were used in this study, data collection process, data prescribing, and data analysis.

3.1. Study design

The design of this study is a record based cross sectional study for a year retrospectively, it is retrospective descriptive and analytical design to compare resistance patterns of UTI bacterial isolates, to antimicrobials among four governmental hospitals in the Gaza Strip, during the period between 1/1/2019 to 31/12/2019, and to assess the SOP intervention, which was introduced at these hospitals on 1/7/2019, This design is chosen because it is the best design to describe the resistance/ susceptibility for antimicrobial situation in governmental hospitals. It is less expensive, and enable the researcher to meet the study objective in a short time. It also studies the whole situation, and the intervention effect retrospectively, and thus provides some possible indication about the future of the bacterial antimicrobial relationship, and consequences. In this study, methodological triangulation would provide combination between quantitative (interviewed questionnaire with laboratory personnel) and qualitative paradigms (in depth interviews and focus groups with health providers and community leaders) to validate findings from one method with another, or to enhance understanding of the facts on the ground.

3.2. Study population and Sample

The study targeted two populations. The first is hospitals that use computerized system, so all data are in a soft copy and are entered by laboratory technicians. The sample included all the records during 1/1/2019 to 31/12/2019.

The second population three focus groups, three key informants, and seven individual interviews have been conducted. In addition, fifteen laboratory technicians responded to a questionnaire, all of them from the microbiology department at the governmental hospitals in the Gaza strip.

3.3. Study setting

The study conducted at four governmental hospitals in Gaza Strip governorates.

- Al-Shifa Hospital
- European Gaza Hospital (EGH)
- Al-Nasser Pediatric Hospital
- Al-Dorra Pediatric Hospital

Two central hospitals selected from two different geographical areas, to reflect representative results. The other two hospitals were pediatric hospitals, in addition to one of the two central hospitals has department for pediatric, were compared with the pediatric hospitals, and all of them are in different geographical area.

3.4. Study Period

The study expected to consume 12 months; it started in September, 2019 and completed by November 2020.

3.5. Eligibility criteria

3.5.1. Inclusion criteria for patients:

•All patients who conducted and registered UTI cultures at the four hospitals, at the period of study.

•All laboratory specialists, technicians' heads of and working in microbiology departments at all governmental hospitals and the director of laboratories in the MOH.

3.5.2. Exclusion criteria for patients:

- All patients who conducted and registered UTI cultures at the four hospitals, out of period of study.
- All patients who conducted and registered cultures other than UTI at the four hospitals, out of period of study.
- Other laboratory technicians at departments other than microbiology in all governmental hospitals.

3.6. Study instrument

In this study the researcher used quantitative and qualitative research, because it is the best for measuring the resistance of bacteria to antimicrobials,

3.6.1. Quantitative part

Data obtained as an excel sheet from laboratory records, UTI cultures results contains susceptibility, resistance to the used antimicrobials, name of the uropathogen, age, gender, date of test, area of living, name of hospital, and diagnosis at the four governmental hospitals, in addition to a questionnaire was conducted among the laboratory specialists and technicians explores dimensions like the availability of logistics to apply the SOP, availability of a written procedure in their hands, facilities presented by administration

(training), anything delays the application of SOP at governmental hospitals, the impact of the SOP on alignment of the work, the impact of the SOP on the results

3.6.2. Qualitative part

Focus groups, key informant and individual informant interviews were conducted to assess the SOP. The questionnaire was conducted for all laboratory technicians at the four hospital, focus groups were conduct for heads of laboratories of the four governmental hospitals, the key informant interview was with the director of the laboratories in the ministry of health.

The first instrument was open question focus group. This focus group was conducted by the researcher within in-depth interviews with heads of the laboratories of the four governmental hospitals. Some of the dimensions are Level of need to this intervention (SOP), professionality of SOP, level of acceptance by the teamwork, training and facilities, challenges to apply it properly, Administration role in respondent point of view in this subject, if they are fulfilling it.

The second instrument was key informant and individual informant interview for the Director of the laboratories and number of the managers of laboratories in the MoH, was open ended (semi-structured) questions the dimensions of the interview are Meaning of this achievement to the MoH,, reasons that rush the MoH to do this intervention (SOP), the reediness of the MoH to launch this intervention (logistics, teamwork, training), Problems tackled after intervention, the effect of intervention on the results, difference between pre and post, the effect on the patient, MoH and community.

3.7. Data collection and processing

3.7.1. Data collection:

Data was already collected during the year by the laboratories technicians whom working at the laboratories of the four governmental hospitals and were given to the searcher as an excel file contains all the recorded cases UTI cultures results contains susceptibility, resistance to the used antimicrobials, name of the uropathogen, age, gender, date of test, area of living, name of hospital, and diagnosis at the four governmental hospitals, the data cleaned, coded and exported to SPSS to be analyzed.

For the questionnaire, focus group and key info the data were collected by the searcher by filling papers and recording audios for interviews and focus group.

3.7.2. Data entry:

Data from the excel file were checked, cleaned, and uploaded into a Statistical Package for Social Sciences (SPSS) file.

For qualitative part the data was coded and analyzed by searcher. The interviews were recorded then the transcript was written, afterward a careful reading for the transcript, and notes were taken, then the relevant pieces were labeled, and coding were created, the coding here is according to the underlying consideration of the pattern, the categories were created, and the data was conceptualized, then results were written.

3.7.3. Data analysis:

Data analysis was done, using SPSS (v. 22). Cross tabulation was made; to detect any correlations, and/or differences among the investigated variables, using chi square, and independent FT test. P-value equal or less than 0.05 was considered statistically significant, with confidence interval (CI) of 95%. Tables, histograms, and charts were

used to present the data. Indicators which used in the study designed to reflect antimicrobial susceptibility situation in governmental hospitals. According to study objectives, some of MoH selected indicators were used including, number and type of antimicrobial used in culture, to determine susceptibility resistance of bacteria to antimicrobial; then calculation of the percentage of resistance result for the same antimicrobial in the same uropathogen in different categories like gender, age, living area, hospital, and diagnosis, Then a comparison was conducted between these variables, to show the difference between the susceptibility and resistance in the same pathogen for the same antimicrobial in different categories like gender, age, living area, hospital, and diagnosis. The instruments that were used are Cross tabulation; to detect any correlations, and/or differences among the investigated variables, chi square, and independent T test.

3.8. Scientific rigor

3.8.1. Quantitative part (questionnaire):

Validity:

The questionnaire was evaluated by experts to assess its relevance and their comments were taken in consideration.

Reliability:

The following steps done to assure instruments reliability

♦ The researchers rehearsed on data collection on the teamwork interviewing steps and the way of asking questions. This ensured standardization of questionnaire filling.

♦ Data entry was done in the same day of data collection which would allow possible interventions to check the data quality or to re-fill the questionnaire when required.

3.8.2. Qualitative part (in-depth interviews):

The followings were done to assure the trustworthiness of the qualitative part in this study. First, a peer check was done through health experts to revise the in-depth interview questions to assure that they covered all the required dimensions. Then, a member check has done to assure accuracy and transparency of the transcripts during the interviews. Prolonged engagement has done as the researcher tried to probe for answers and cover all the interview dimensions properly. In addition, recording the interviews enhanced tracking up facts and re-check the accuracy of the transcripts. Finally, all the transcripts and recordings were kept for tracking the information by others at any time (Audit trail).

3.9.Ethical Consideration procedures and permissions

The researcher has obtained a verbal approval from human resources development in Gaza Strip, to use the microbiology data from four hospitals (only urine culture results). A formal application was presented along with this study after approval. A soft copy (and excel file was obtained).

The researcher was keen committed to all ethical considerations required to conduct a research. First, ethical approval was obtained from both the school of public health Al-Quds University and Helsinki Committee to carry out the study. Second, a permission to use the microbiology data was obtained from the director general of human resources development in Gaza Strip.

Chapter Four

Results and Discussion

In this chapter, results of data analysis are presented and discussed, these results include frequency of uropathogens isolates, the resistance of different isolates to different antimicrobials, comparison between genders, age groups, and hospitals, pre-and post-implementation of the SOP. In addition, the results of the focus group and key informant's interviews are summarized and presented.

4.1 Frequency of uropathogens isolation

The records of 11,890 urine samples were received from four governmental hospitals in the Gaza Strip-Palestine. Only 2,910 (24.5%) exhibited significant growth and were considered as positive for UTIs. This is lower than the result of a study from South India, which showed that 38.9% of the urine samples were culture positive (Somashekara, et al., 2014).

The frequency and percentage of common Gram-negative (91.8%) and Gram-positive (5.25%) urinary pathogen resistance to the antimicrobial agent is shown in Table (4.1), a study in Lahore, Pakistan was conducted Between December 2018 and June 2019, showed that prevalence of Gram negative was (92%) (Asmat, U.et al.,2020), another study in Ethiopia reveled that Gram-negative bacteria cause 90% of UTI cases while gram-positive bacteria cause only 10% of the cases (Seifu, W. D., & Gebissa, A. D. (2018)).

Among the uropathogens isolated during the data collection period, *E. coli* constituted the majority with 59.9% followed by *Klebsiella* spp. (24.9%), *Pseudomonas* spp. (4.2%), and *Proteus* spp. (2.4%). Gram-negative constitutes 91% of the isolates, Gram-positive (*S. aureus, Enterococci*, and *Streptococcus* spp.) constituted less than 5.5%, while less than

3% of the isolates were classified as "others" as shown in Table (4.1). In North Ethiopia, *E. coli* prevalence in UTI was 60.29% and *Klebsiella* spp. prevalence was 5.88% in a study conducted from 2002 to 2011 (Abejew, et al.,2014). Another study reported 79% *E. coli* prevalence in UTI in Luxembourg (Saperston, et al., N., 2014).

Table 4.1: The frequency of uropathogens isolates at four governmental hospitals during the period between 1/1/2019 to 31/12/2019 in the Gaza Strip-Palestine

Organism isolated (n=2,910)	Frequency	Percentage	Total
Escherichia coli	1,743	59.9	Gram negative 2672 (91.8%)
Klebsiella spp.	725	24.9	
Proteus spp.	69	2.4	
Enterobacter spp.	12	0.4	
Pseudomonas spp.	123	4.2	
Staphylococcus aureus	41	1.4	Gram positive152 (5.25%)
Enterococci	13	0.4	
Streptococcus spp.	98	3.4	
Candida spp.	70	2.4	Others 86 (2.95%)
Others	16	0.5	
Total	2,910	100	2910 (100%)

4.2 Prevalence of UTI among male and female

Females represented 71.4% of all positive urine cultures with an odds ratio of 1.863 (**Figure 1**). These results are in accordance with well-established literature around the world. Several studies reported higher frequency in females than males, one of them is at a central hospital in Libya (Mohammed, et al., 2016), and the other is at Qassim University in Saudi Arabia (Ahmed, et al., 2019), and a third study was in India (Hasan, et al., 2007**).**

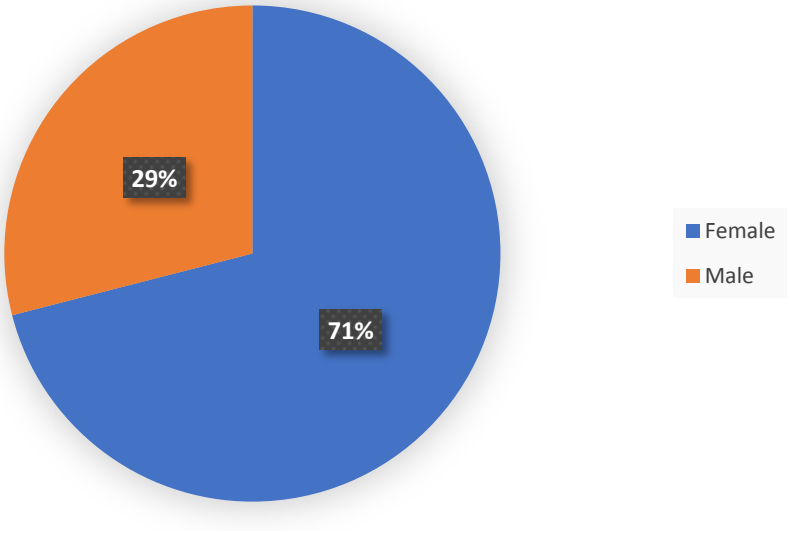


Figure 4.1: Distribution of UTIs according to gender at four governmental hospitals in the Gaza Strip- Palestine 2019

4.3 The resistance uropathogens to tested antimicrobials

This section describes the resistance pattern of microorganisms to the antimicrobials**.** The findings listed in Table (4.1) shows the susceptibility patterns *E. coli* and *Klebsiella* spp., which constituted about 85% of the total isolates, and both of them are the main etiologic to UTI, the discussion will include both of them. In addition, the susceptibility profiles of all other uropathogens are illustrated for the tested antimicrobials.

A prominent finding is the high resistance exhibited by uropathogens to penicillin group. The resistance to penicillin derivatives like ampicillin was 91% and amoxicillin was 90% for *E. coli*, and the resistance is 95% for *Klebsiella* spp. for the same antimicrobials.

As shown in Table (4.2), *E. coli* is highly resistant to the cephalosporin group. Its resistance is between 41% and 60% against all of the cephalosporines, *E. coli* has the highest resistance against cephalexin (60%) and the lowest resistance against ceftazidime (41%) among the cephalosporin group. *Klebsiella* spp. has resistance (73%) and (49%) against the same antimicrobials respectively.

But in the UK the resistance for amoxicillin was less than 49%, and cefuroxime less than 4% (Farrell, et al., 2003). These organisms are not susceptible to these antimicrobials. A

further study from Iraq in 2016 finding is that the resistance to *E. coli* is not so far from this study, the resistance is 100% for penicillin and 52% for cephalosporin (Polse, 2016). In Saudi Arabia, the resistance of *Klebsiella* spp. was 91% against ampicillin, 57% against cefotaxime, and 46% against ceftazidime (Taher, 2019).

Table 4.2: Resistance pattern of uropathogens to antimicrobials at the four governmental hospitals in the Gaza Strip- Palestine during 2019

Antimicrobial	***E. coli***	***Klebsiella* spp.**	***Proteus* spp.**	***Enterobacter* spp.**	***Pseudomonas* spp.**	***S. aureus***	***Enterococci***	***Streptococcus* spp.**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Penicillin G	3 (100)	7 (100)	-	-	1 (100)	3 (75)	4 (36)	1 (100)
Ampicillin	553 (91)	245 (95)	27 (90)	5 (100)	30 (100)	3 (60)	3 (30)	5 (100)
Amoxicillin	154 (90)	70 (95)	13 (87)	4 (100)	7 (88)	5 (71)	1 (100)	2 (67)
Cloxacillin	5 (100)	1 (50)	-	-	-	5 (50)	-	19 (79)
Piperacillin	148 (74)	90 (79)	2 (50)	1 (50)	19 (79)	-	-	-
Cephalexin	540 (60)	279 (73)	21 (68)	2 (67)	42 (91)	2 (15)	4 (67)	29 (74)
Cefuroxime	682 (49)	350 (62)	20 (37)	3 (33)	63 (81)	6 (26)	7 (64)	24 (47)
Cefotaxime	474 (44)	267 (60)	10 (24)	-	29 (43)	2 (67)	4 (57)	-
Ceftazidime	494 (41)	243 (49)	18 (45)	1 (20)	36 (38)	1 (50)	7 (100)	-
Ceftriaxone	681 (46)	364 (59)	16 (29)	2 (22)	49 (49)	3 (50)	5 (56)	-
Cefazolin	344 (53)	154 (61)	10 (34)	4 (50)	32 (84)	3 (75)	1 (50)	-
Doxycycline	304 (59)	151 (66)	16 (80)	0 (0)	41 (85)	4 (29)	-	
Amikacin	15 (2)	14 (4)	1 (3)	-	5 (8)	1 (17)		-
Gentamicin	321 (23)	172 (29)	20 (38)	4 (40)	23 (24)	8 (30)	7 (54)	25 (48)
Co-Trimoxazole	959 (66)	420 (69)	47 (80)	8 (80)	78 (91)	14 (54)	4 (67)	46 (78)
Nalidixic acid	852 (53)	330 (50)	37 (63)	3 (30)	87 (84)	1 (33)	5 (100)	4 (100)
Ciprofloxacin	450 (35)	198 (38)	16 (34)	4 (40)	36 (36)	12 (38)	7 (70)	45 (63)
Rifampicin	-		-	-	-	1 (3)	-	27 (36)
Vancomycin		-	-	-	-	8 (21)	2 (18)	17 (18)
Co-amoxiclav	45 (73)	17 (68)	5 (63)	-	3 (75)	13 (45)	1 (50)	32 (42)
Meropenem	24 (6)	16 (8)	3 (14)	1 (25)	11 (20)	0 (0)	1 (50)	-
Nitrofurantoin	20 (15)	24 (44)	2 (50)	0 (0)	8(73)	-	-	-
piperacillin + tazobactam	13 (9)	9 (11)	0 (0)	0 (0)	0 (0)	-	-	-
Total R (%)	7082(45)	3422(53)	284(46)	42(40)	600(56)	95(33)	68(56)	288(49)
- This antimicrobial did not used for this microorganism 0(0) This microorganism is 0% resistant to antimicrobial								

As presented in Table (4.2), the resistance of *E. coli* against co-amoxiclav is 73%, meropenem is 6%, nitrofurantoin is 15%, and nalidixic acid is (53%). The resistance of

Klebsiella spp. against co-amoxiclav is 68%, meropenem (8%), nitrofurantoin (44%), and nalidixic acid (50%)., the resistance of *E. coli* against co-trimoxazole was 66%, and 69% against *Klebsiella* spp.

In our study, the resistance of *E. coli* against ciprofloxacin is 35% and the resistance of *Klebsiella* spp. is 38%. The resistance *of E. coli* in this study against gentamicin is 23% and in *Klebsiella* spp., the resistance is 29%. Both of *E. coli* and *Klebsiella* have the minimal resistance against amikacin, which are (2%) and (4%) respectively. But in the UK, Nitrofurantoin was very active against isolates of *E. coli* (96.3% susceptible) and the resistance against amoxicillin was higher (48%) (Farrell D., et al., 2003) and about (30%) in Rohtak, India (Gupta, N. et al., 2007).

Another study from India revealed that *E. coli* resistance against amikacin was (38-16%), followed by cefotaxime (40-38%), gentamicin (68-42%), ciprofloxacin (73-54%), and co-trimoxazole (90-74%) in the period between 2000 and 2004 (Gupta, et al., 2007).

A study in Arabia Saudi found that the resistance of *E. coli* against meropenem was 7%, amikacin (9%) and gentamicin (18%) (Taher, et al., 2019). In south Iran, a study conducted in 2019 found that the resistance of *E. coli* against nalidixic acid was 71.9% (Malekzadegan, et al.,2019). In Rajasthan, a study conducted in 2012 recorded an overall resistance of *E. coli* against nalidixic acid, norfloxacin, and ciprofloxacin as (94%), (77%), and 74.75%, respectively (Sood, & Gupta, 2012).

Ciprofloxacin was highly active against *E. coli* with susceptibilities between (88%) and (97%) and against the most prevalent pathogens (Farrell et al., 2003). In south India, *E. coli* was least resistant against imipenem (8%) and amikacin (16%), moderate against ceftazidime (36%), and showed a high resistance pattern against co-trimoxazole (69%), fluoroquinolones, and ampicillin (86%). *Klebsiella* spp. were least resistant against

amikacin (26%), moderate against cephalosporins and fluoroquinolones, and highly resistant against ampicillin (92%). (Somashekara, et al., 2014).

In Turkey, a study reviewed the resistance of microorganism in period between 1998 and 2003, it revealed that the resistance of *E. coli* during these years against co-trimoxazole was increased by the time from (37.1% to 44.6%) (Kurutepe, et al., 2005), in addition, higher resistance rates against ampicillin and co-trimoxazole were found in other countries, including Senegal (77% and 55%) (Dromigny, et al., 2002), Spain (65% and 33%) (Gutierrez, et al., 2001, and in Taiwan (80% and 50%) (Lau, 2004) respectively.

These variations may be due to different geographical settings of these studies, use or misuse of antimicrobials, treatment protocols, and study sample size among many other causes.

There were clear violations of the SOP instructions, particularly with regard to the usage of some antimicrobial. For instance, using aminoglycosides (Amikacin, Gentamicin) and Cephalosporins third-generation (ceftazidime, cefotaxime) for gram-positive isolates and using Vancomycin and Rifampicin for gram-negative (Table 4.).

Vancomycin and rifampicin are not used for *Enterobacteriaceae* (*E. coli* and *Klebsiella* spp.) before and after the SOP implementation but it is recommended for Gram-positive bacteria only, and it is used for *Streptococcus* spp. pre- and post-SOP normally.

4.4 Comparison *E. coli* and *Klebsiella* spp. resistance against antimicrobials among the four governmental hospitals

This section summarizes the difference between the antimicrobial resistance *of E. coli* and *Klebsiella* spp. among the four governmental hospitals. In **Figure (4.2)**, *E. coli* at Al-Shifa Hospital has the highest resistance against the following antimicrobials (gentamicin (40%), ciprofloxacin (58%), ceftriaxone (62%), cefuroxime (69%), nalidixic acid (71%), and

amoxicillin (100%)). *E. coli* at both of Al-Nasser and Al-Dorra Hospitals have almost identical resistance against these antimicrobials (Gentamicin (9%), Ciprofloxacin (12%), ceftriaxone (32%), cefotaxime (33%) cefuroxime (39%), nalidixic acid (40%),) while at Al-Dorra Hospital, *E. coli* is less resistant against cephalexin than Al-Nasser Hospital.

At Al-Dorra Hospital, the resistance of *E. coli* against amoxicillin (90%) is higher than both Al-Nasser and European Hospital but Al-Shifa still highest.

Figure (4.3) records that *Klebsiella* spp. has the highest resistance against these antimicrobials (meropenem (11%), gentamicin (42%), ciprofloxacin (54%), nalidixic acid (65%), ceftriaxone (70%), cefuroxime (72%), and amoxicillin (100%)) at Al-Shifa Hospital. *Klebsiella* spp. has highest resistance against these antimicrobials (Nitrofurantoin 75%, co-trimoxazole 78%, and cephalexin 88%) at European Hospital. *Klebsiella* spp. has the lowest resistance against these antimicrobials (ciprofloxacin (7%), gentamicin (16%), nalidixic acid (29%), ceftriaxone (42%), cefotaxime (42%), cefuroxime (51%), cephalexin (63%), and amoxicillin (91%)) at Al-Dorra Hospital.

Klebsiella spp. resistance at Al-Nasser Hospital is slightly higher than Al-Dorra Hospital Isolates, then European Hospital is higher than both of them, and Al-Shifa Hospital is the highest.

Both comparisons reveal that Al-Shifa Hospital has the highest resistance against most of the antimicrobials, which means that there are common causes that contribute either to emergence or spread of the microorganism resistance against the antimicrobials extensively at this hospital more than other hospitals. Al-Dorra hospital generally has the isolates with the lowest resistance against the antimicrobials.

We can rank the hospitals according to resistance against the antimicrobials from the lowest resistance to the highest resistance Al-Dorra Hospital then Al-Nasser Hospital the European Hospital and the highest resistance is Al-Shifa Hospital.

These findings can lead to concluding that the resistance of microorganisms vary from one hospital to another and from place to place. This calls for further studies to determine the

factors contributing to the increase resistance in general and at Al-Shifa Hospital in particular.

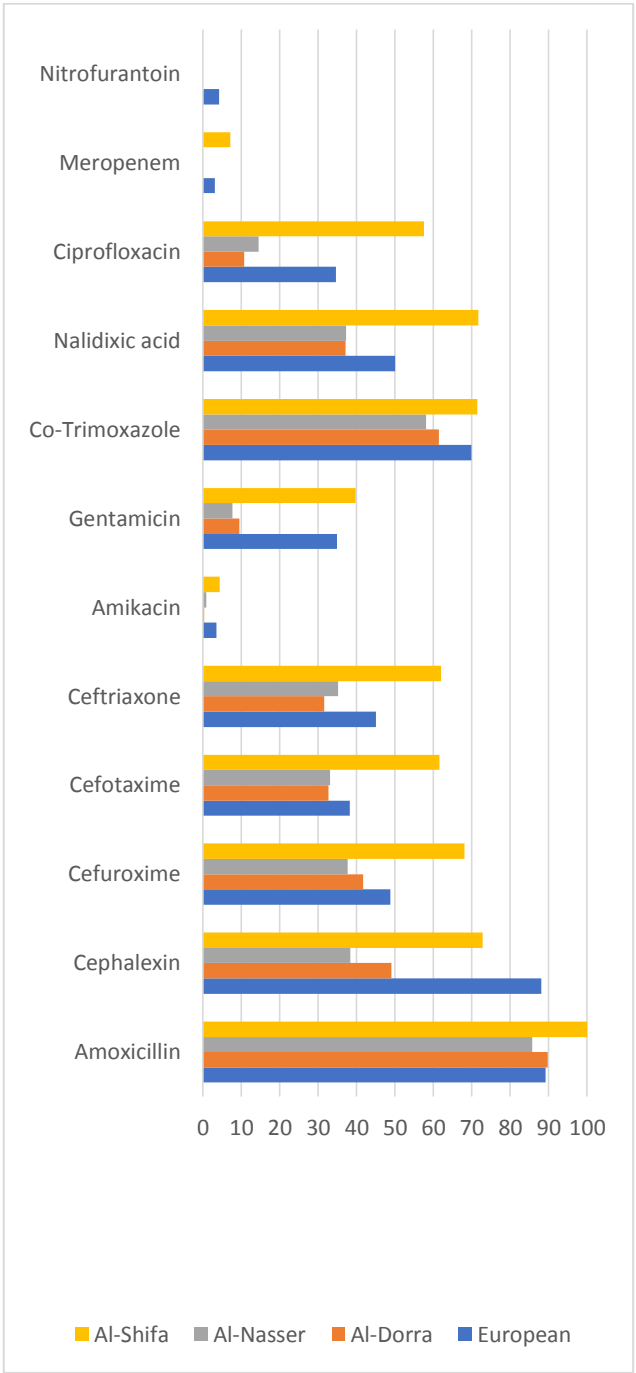


Figure (4.2) Resistance of *E. coli* to antibiotics in different governmental hospitals in the Gaza Strip-Palestine

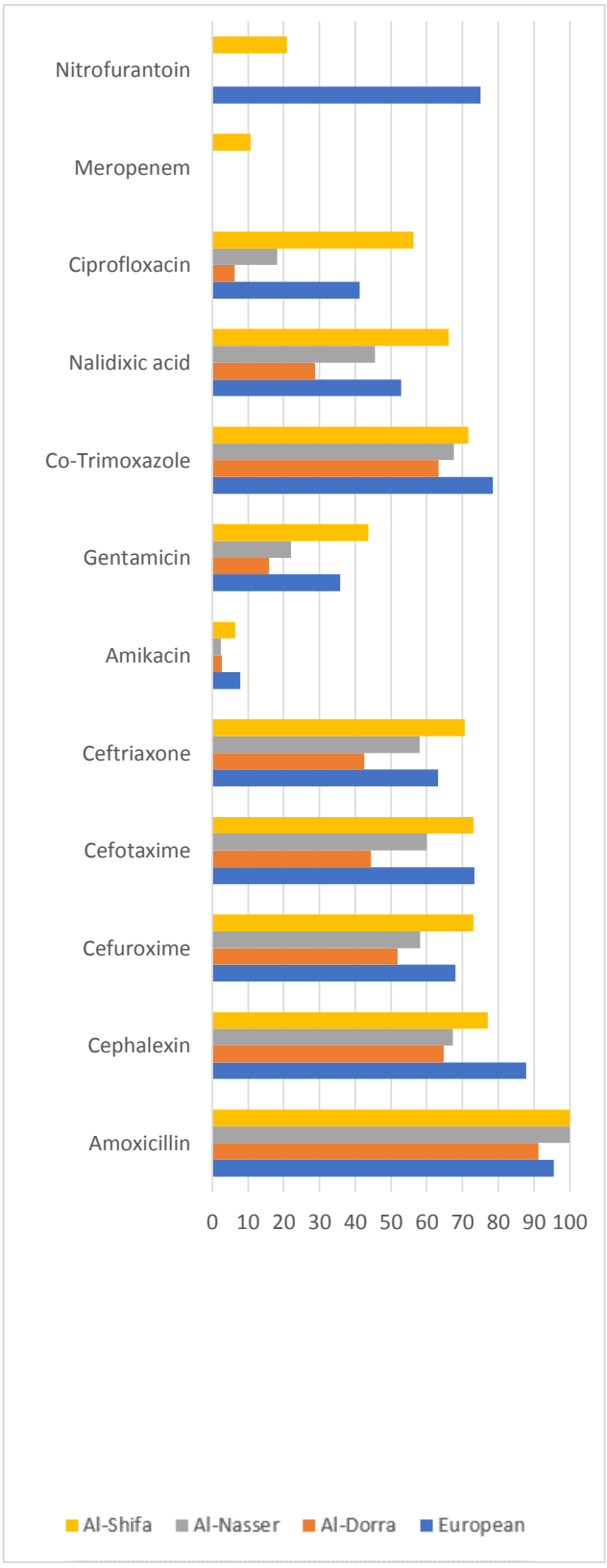


Figure (4.3) Resistance of *Klebsiella* to antibiotic in different governmental hospitals in the Gaza Strip-Palestine 2019

4.5 Comparison between different uropathogens and gender:

As shown in Table (4.3), the total resistance of *E. coli* to all antimicrobials in females is 43% while in the male it is 53%. In addition, the total antimicrobial resistance of *Klebsiella* among female isolates is 51% while in males 57%. Despite higher prevalence of UTI in the female than in males (Table 4.1), the resistance percentage against antimicrobial is higher in male than in the female.

According to Daza, (2001) and Dromigny et al., (2002), this phenomenon may be attributed to the histology, anatomy, and physiology of female and male urinary tract, the morphology difference and difference between etiologies of UTI in both sexes. Among females, most cases range from mild to moderate and may be as a result of pregnancy or hygiene problems. But in males, it is completely different, most of the time the etiology is complicated, maybe stroke or paraplegia or quadriplegia and many times the patient is on a folly catheter fixation or clean intermittent catheterization, which may cause infection for males that is many times chronic. Such patients are usually prescribed several antimicrobial regimens. This also needs further large and specific studies to determine the main causes of this phenomenon.

By conducting independent T-test for all antimicrobials, P. values is statistically significant only for co-amoxiclav (P. value= 0.006) and marginally significant for piperacillin (P. value= 0.052) and the total antimicrobial resistance was statistically significant (P. value= 0.024) as shown in Table (4.3).

Several risk factors are associated with UTIs, including gender. The shorter distance to the bladder in women makes it easier for bacterial colonizers to reach it (Fox-man, 2010). Male patients, conversely, have a lower risk of contracting uncomplicated UTIs but are more prone to contracting complicated or MDR infections (Schaeffer and Nicolle, 2016).

Our data reflect the severe nature of UTI in men, in which infections are caused by more dangerous and infectious MDR microorganisms than in female patients.

Table 4.3: Antimicrobials resistance of uropathogens according gender at the four governmental hospitals in the Gaza Strip- Palestine during 2019

Isolate	***E. coli***		***Klebsiella* spp.**		***Pseudomonas* spp.**		***Proteus* spp.**		**P. value**
Antimicrobials	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	
Ampicillin	428(90)	125(94)	150(94)	95(97)	12(100)	18(100)	19(86)	8(100)	0.164
Amoxicillin	121(90)	33(89)	43(93)	27(96)	2 (67)	5(100)	10(83)	3(100)	0.087
Piperacillin	107(70)	41(85)	57(73)	33(92)	10(77)	9(82)	1(33)	1(100)	0.052
Cephalexin	388(57)	152(69)	177(71)	102(78)	19(90)	23(92)	10(53)	11(92)	0.188
Cefuroxime	483(45)	199(62)	219(59)	131(66)	28(76)	35(85)	10(29)	10(53)	0.282
Cefotaxime	333(41)	141(53)	165(58)	102(63)	14(41)	15(45)	6(22)	4(27)	0.562
Ceftazidime	330(37)	164(52)	158(48)	85(53)	17(35)	19(40)	12(43)	6(50)	0.105
Ceftriaxone	473(42)	208(56)	233(56)	131(65)	18(38)	31(60)	10(28)	6(30)	0.272
Cefazolin	248(50)	96(64)	97(58)	57(68)	14(78)	18(90)	6(27)	4(57)	0.242
Amikacin	7(1)	8(4)	6(3)	8(6)	2(8)	3(8)	1(4)	0(0)	0.832
Gentamicin	225(20)	96(30)	113(29)	59(30)	11(23)	12(25)	13(38)	7(37)	0.545
Doxycycline	206(57)	98(63)	113(65)	38(69)	19(83)	22(88)	12(75)	4(100)	0.367
Co-Trimoxazole	731(66)	228(66)	291(69)	129(71)	36(86)	42(95)	29(73)	18(95)	0.389
Nalidixic acid	608(50)	244(62)	226(51)	104(48)	43(84)	44(83)	24(60)	13(68)	0.722
Ciprofloxacin	292(30)	158(48)	136(38)	62(38)	21(40)	15(31)	9(30)	7(41)	0.299
Co-amoxiclav	35(71)	10(77)	15(65)	2(100)	2(67)	1(100)	3(50)	2(100)	0.006
Meropenem	15(6)	9(8)	12(9)	4(7)	5(17)	6(23)	3(20)	0(0)	0.572
Nitrofurantoin	15(15)	5(14)	13(34)	11(69)	1(33)	7(88)	2(50)	0(0)	0.678
Piperacillin + tazobactam	8(7)	5(14)	6(10)	3(13)	0(0)	0(0)	0(0)	0(0)	0.610
Total	5053(43)	2020(53)	2230(51)	1183(57)	274(54)	325(60)	180(44)	104(59)	0.024

4.6 Resistance of uropathogens according to age category

As shown in Table (4.4), there is fluctuation in the resistance of the microorganisms against antimicrobials in different age groups. ANOVA test was used to determine the significance of this variation. The result of ANOVA revealed that the fluctuation among age categories is statistically significant for number of antimicrobials (e.g., Ampicillin,

piperacillin, cefotaxime, cefazolin, amikacin, gentamicin, nalidixic acid, ciprofloxacin, and piperacillin + tazobactam) with a P. value of < 0.05). Two antimicrobials (cephalexin and ceftriaxone) with a P. value of 0.05, while other antimicrobials were not statistically significant (e.g., cefuroxime, amoxicillin, ceftazidime, doxycycline, co-trimoxazole, co-amoxiclav, and nitrofurantoin).

when we conducted scheffe test, to recognize these fluctuations and to find a correlation among these age groups, we found that there is a prominent correlation between age group 0-28days group and adult group with (P. value) less than .05 like (cefuroxime, ampicillin, amoxicillin, piperacillin, cephalexin, cefazolin, gentamicin, co-trimoxazole, nalidixic acid, and ciprofloxacin) but we did not find clear correlations among the others Table (4.4).

From these results, it can be concluded that there is fluctuation in resistance of the isolate to the antimicrobial according to the age, but the pattern is not clear. Since there is no clear trend in this fluctuation of resistance among age groups, further studies to determine the nature of this fluctuation or adding other factors may boost the correlation or find a confounder.

A study conducted in Pakistan in 2008 gave similar results, it reported variations among age groups with regard to resistance and it appeared that in the case of males, *E. coli* isolates were susceptible to nitrofurantoin in age groups 0+, 50+, and 70+, while in age groups 20+, 30+ and 60+ hundred percent resistance was recorded. *E. coli*. In females, showed no resistance to

Table 4.4: Percentage of antimicrobial resistance of all microorganisms at the four governmental hospitals distributed by age groups in the Gaza Strip-Palestine 2019

Antimicrobials	Age groups				ANOVA P. value	Scheffe test P. Value
	0-28 day	29d-1 year	1-12 y	Adult		
	R (%)	R (%)	R (%)	R (%)		
Cefuroxime	22 (47)	99 (46)	463 (44)	577 (66)	0.300	.012
Ampicillin	30 (97)	86 (91)	485 (90)	277 (96)	0.046	.010
Amoxicillin	4 (80)	45 (92)	115 (91)	97 (90)	0.162	.003
Piperacillin	0 (0)	22 (73)	91 (61)	149 (89)	0.000	.009
Cephalexin	16 (53)	52 (60)	331 (54)	524 (75)	0.052	.013
Cefotaxime	13 (43)	57 (39)	279 (37)	441 (62)	0.035	.077
Ceftazidime	12 (40)	39 (35)	201 (32)	554 (50)	0.069	.303
Ceftriaxone	13 (46)	92 (44)	353 (35)	667 (63)	0.056	.052
Cefazolin	8 (42)	57 (53)	192 (44)	295 (69)	0.008	.015
Amikacin	1 (3)	6 (4)	14 (2)	22 (6)	0.036	.416
Gentamicin	7 (16)	24 (12)	146 (14)	407 (41)	0.000	.002
Doxycycline	6 (67)	7 (64)	12 (52)	504 (62)	0.097	.274
Co-Trimoxazole	26 (60)	131 (67)	564 (63)	859 (73)	0.436	.002
Nalidixic acid	17 (39)	78 (36)	394 (38)	835 (71)	0.000	.004
Ciprofloxacin	5 (16)	20 (15)	120 (15)	627 (55)	0.000	.000
Co-amoxiclav	2 (100)	11 (69)	37 (71)	68 (46)	0.815	.134
Colistin	0 (0)	17 (85)	106 (60)	9 (28)	0.000	.870
Meropenem	1 (50)	1 (5)	0 (0)	56 (10)	0.000	.371
Nitrofurantoin	1 (25)	2 (33)	4 (13)	49 (29)	0.984	.567
piperacillin + tazobactam	0 (0)	5 (21)	11 (10)	6 (5)	.011	.896
ANOVA P. value: among all age groups			Scheffe test P. Value between 0-28 days group & adult group			

nitrofurantoin in age groups 10+, 50+, and 70+, while it showed 33% resistance in age groups 0+, 20+, and 30+. *E. coli* isolates from age groups 50+ and 70+ both in males and females were found to be 100% susceptible to the nitrofurantoin (Bashir, et al., 2008).

A study conducted in California State University concluded that antibiotics that target DNA synthesis result in a progressively higher number of resistant isolates among the

older population. The results emphasize the importance of patient age on antibiotic selection as a preventive measure to reduce the rate of resistant infections in each susceptible population. This pattern suggests that physicians should take into consideration patient age as another factor in determining the best antibiotic regiment with the aim of curtailing the emergence of newer resistant phenotypes in the future (Garcia, A., 2017)

4.7 Comparing resistance according to gender and age

E. coli isolates were grouped according to age and gender, the difference is high between males and females in the age category of (0-28 days). Within the age category (29 days to 1 year), the resistance in females is higher than in males for most of the antimicrobials. However, in the age categories (1year to 12 years) and adults, the resistance is higher in males to most of the antimicrobials than in females.

As shown in **Figure (4.4),** *E. coli* resistance to antimicrobials among male isolates is higher than females isolate in most of the age categories. In the age category (0-28 days), *E. coli* isolates were resistant to amoxicillin is closed 100% in both genders. There is a difference in resistance of the *E. coli* against these antimicrobials (cephalexin, ceftazidime, ceftriaxone, and cefuroxime) in this age category about 30-40% between genders, However, both co-trimoxazole, and nalidixic acid show resistance in females, is higher than males in this age category.

Among the age category (29 days to 1 year), *E. coli* in males is more resistant than in female against amoxicillin, cephalexin, and cefotaxime, while the resistance in female is higher than males against ceftazidime, gentamicin cephazolin, co-trimoxazole, Nalidixic acid, and piperacillin **(Figure 4.5).**

In the age category (1year to 12 years), *E. coli* resistance in males is higher than in females against piperacillin, cephalexin, cefuroxime, cefotaxime, ceftazidime, cefazoline, nalidixic acid, and ciprofloxacin. The resistance of *E. coli* in female isolates higher than male

against amoxicillin and co-trimoxazole. The resistance of *E. coli* to gentamicin is almost the same **(Figure 4.6).**

In the age category, (adults) the resistance of *E. coli* in male is higher than in female against the all of the antimicrobials (amoxicillin, piperacillin, cephalexin, cefuroxime, cefotaxime, ceftazidime, ceftriaxone, cefazolin, gentamicin, co-trimoxazole, nalidixic acid, ciprofloxacin) **(Figure 4.7).**

A prominent finding is the high resistance exhibited by uropathogens among male isolates in most of the age categories.

A study in southwest Washington in 2013 showed statistically significant differences between males and females in the age-specific susceptibilities of *E. coli* to ampicillin, co-amoxiclav, ciprofloxacin, and nitrofurantoin. Urinary *E. coli* isolates from male patients tend to exhibit increased antimicrobial resistance than isolates from female patients. Despite the statistical significance of time trends and differences in age-specific susceptibilities, the magnitude of these differences was generally less than 5% and thus may not represent clinically meaningful differences. The exception was susceptibility to amoxicillin-clavulanate, where susceptibility was roughly 10% lower in males aging 18 to 64 years than females in the same age group (McGregor, et al., 2013). A 10-year study of community UTI in Portuguese patients also identified differences in antimicrobial susceptibility according to patient gender. The authors reported that urinary isolates of *E. coli* were significantly more resistant to fluoroquinolones, penicillin's, nitrofurantoin, and first and second-generation cephalosporins among men compared to women (Linhares, et al., 2013).

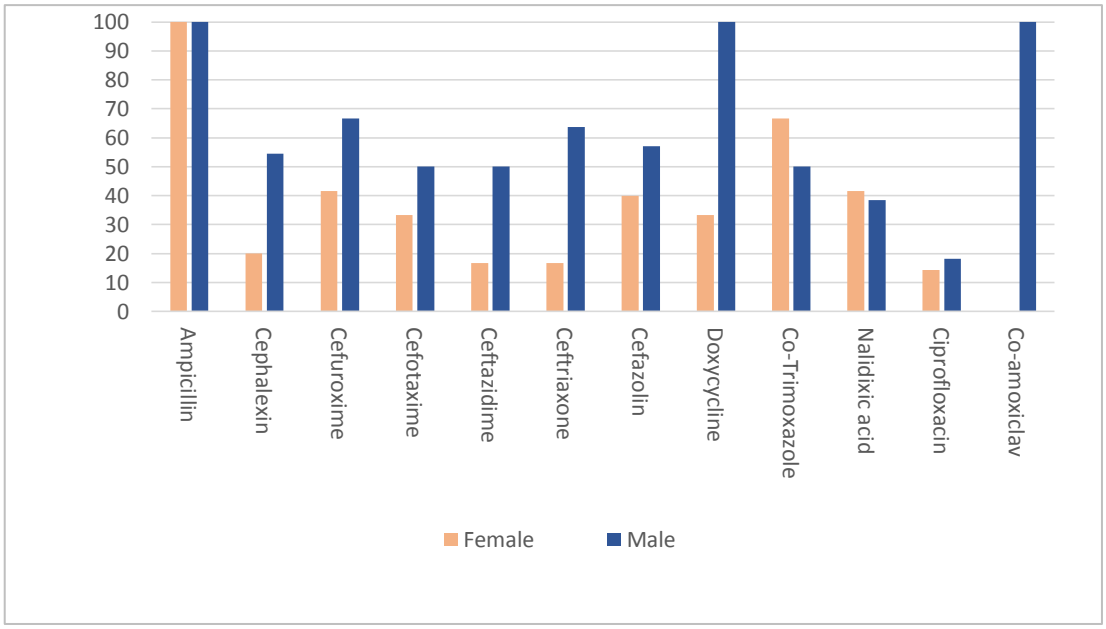


Figure (4.4): *E. coli* resistance percentage to antibiotics 0-28 days male and female

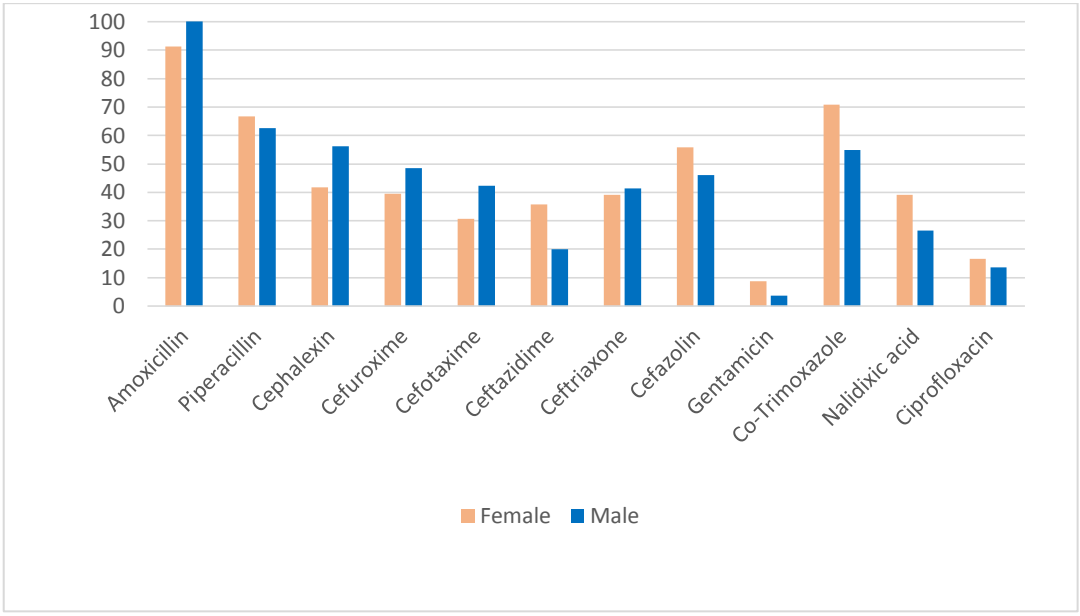


Figure (4.5) *E. coli* resistance percentage to antimicrobial male female 29 days-1year

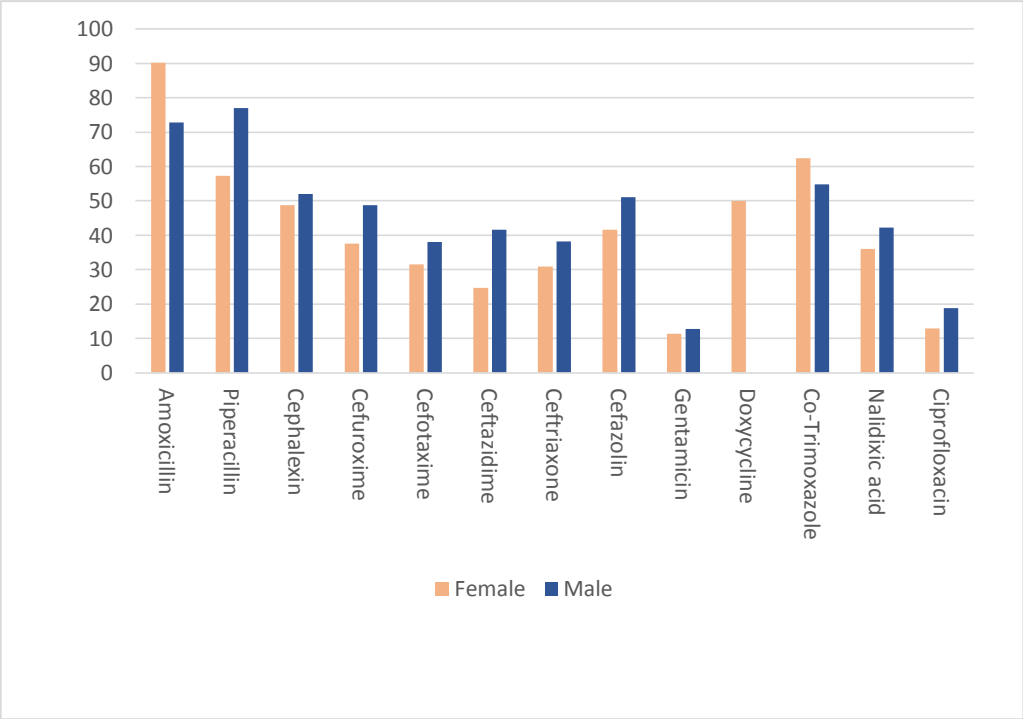


Figure (4.6) *E. coli* resistance percentage to antimicrobial male female 1-12 years

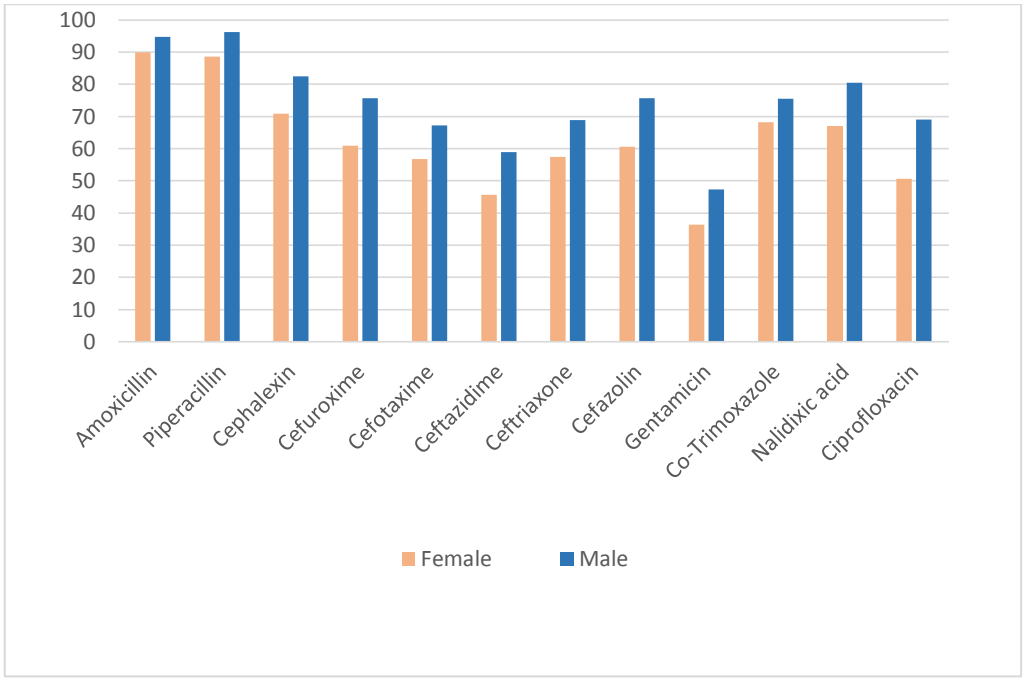


Figure (4.7) *E. coli* resistance percentage to antimicrobial male and female adult

Another study focused on pediatric patients, also identified significantly higher resistance to co-trimoxazole and ciprofloxacin in male versus female patients (Edlin, et al., 2013).

The NAUTICA surveillance study of outpatient UTIs, reported greater antimicrobial resistance to ciprofloxacin, levofloxacin, and co-trimoxazole among all urinary isolates from U.S. and Canadian male patients (Zhanel, et al., 2005). In the CANWARD study, antimicrobial susceptibility among all *E. coli* isolates (not limited to urine isolates) collected from Canadian tertiary medical centers were compared and resistance was also observed to be significantly higher to ciprofloxacin, levofloxacin, and co-trimoxazole in isolates collected from male patients versus female patients (Lagacé-Wiens, et al., 2011).

Most studies of urinary tract infections (UTIs) focus on female patients because of the higher incidence in women than in men. For this reason, most UTI guidelines are based on studies performed among women, despite the obvious genito-urinary differences (Koeijers, J. J.,2007). In men, UTIs become increasingly frequent with age and functional disability, but bacteriuria in elderly men tends to be intermittent, episodic, and more complex to diagnose. It is generally recognized that treatment recommendations for women are not usually appropriate for men. However, guidelines or recommendations for the man–agement of men are mostly based on studies in women, children and institutionalized elderly people of both sexes (Hummers-Pradier, E.,2004).

4.8 Assessing the adherence of laboratory staff of using the required antimicrobials

The extent of adherence to the SOP instruction of testing specific antimicrobials against specific isolates (Chapter 2, pages 25, 26, 27), was evaluated. The indicator used to show the level of adherence of the laboratory technicians to the SOP, is the frequency of using the antimicrobial to the frequency of isolate appearance in the samples.

According to table (4.5), there was a considerable adherence to the SOP instructions in using the following antimicrobials against *Enterobacteriaceae* isolated from pediatric patients e.g., cefuroxime (from 96% to 97%), ceftazidime (37% to 76%), cefazoline (22% to 61%), amikacin (51% to 88%) and gentamicin (88% to 95%). The adherence to the SOP among adults' isolates also improved in cefotaxime (from 19% to 85%), ceftazidime (75% to 91%), ceftriaxone (69% to 90%), cefazoline (22% to 41%), and amikacin (7% to 48%).

Adherence to the SOP in the following antimicrobials against Enterobacteriaceae, for pediatrics, decreased considerably for amoxicillin (from 70% to 23%), cefotaxime (82% to 54%), and co-trimoxazole (88% to 78%). The adherence to the SOP in adults decreased for amoxicillin (from 43% to 3%), cefuroxime (66% to 55%), gentamicin (92% to 51%), doxycycline (from 84% to 38%), co-trimoxazole (from 89%to 79%), nalidixic acid (from 95% to 85%), and ciprofloxacin (from 88% to 68%).

The percentage of cephalexin usage decreased for *Enterobacteriaceae* in pediatrics from 74% to 31% and in adult from 62 % to 38%, after implementation of the SOP (table 4.5). Cephalexin was the least effective within the cephalosporin group and according to the percentage of usage in the cultures and the instruction of the SOP, the cephalexin it is not recommended to be used in *Enterobacteriaceae* (*E. coli* and *Klebsiella* spp.).

Piperacillin was not used before the SOP implementation, and it is not recommended by the SOP, yet after SOP implementation, the use of piperacillin increased for *Enterobacteriaceae* in pediatric from 0% to 27% and in adult from 0% to 22 %. It should be noted that, *E. coli* and *Klebsiella* spp. has high resistance against piperacillin, which is 74% and 79% respectively.

Variable levels of adherence exhibited by the microbiology laboratory staff in using most of cephalosporines like (cefuroxime, cefotaxime, ceftazidime, ceftriaxone, and cefazoline)

and in avoiding the use of certain penicillin's like (amoxicillin and cloxacillin) in *Enterobacteriaceae* isolates as shown in table (4.5).

E. coli showed 66% resistance to Co-trimoxazole and 53% to nalidixic acid, while *Klebsiella* spp. showed 69% and 50% resistance to the same drugs respectively (Table 4.3). Both antimicrobials are recommended for *Enterobacteriaceae* and they were used extensively before and after SOP implementation (Table 4.5). The high resistance exhibited against both drugs calls for periodical review of the SOP and the list of recommended antimicrobials should be changed based on local results review.

The use of meropenem was dramatically increased after SOP implementation from 5% to 73% for the adults with *Enterobacteriaceae*. Nitrofurantoin and tazobactam use seem to be in harmony with the SOP recommendations.

Despite the fact that colistin is not recommended in the SOP for *E. coli* and *Klebsiella* spp., and was not used before SOP implementation, yet it was used after SOP implementation against 31% of the tested *Enterobacteriaceae*. Another issue that should be pointed out, is that colistin

Table (4.5): Antimicrobials usage for common isolates pre- and post-SOP implementation at the four governmental hospitals in the Gaza Strip -Palestine 2019

Isolate	***Enterobacteriaceae***				***Pseudomonas* spp.**				***Streptococcus* spp.**	
Frequency of Isolate	692	622	569	654	11	23	34	55	56	41
Age category of patient	Pediatrics		Adult		Pediatrics		Adult		Adult	
The time regarding SOP implementation	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Ampicillin	70%	23%	43%	3%	82%	35%	35%	2%	9%	0%
Amoxicillin	23%	2%	13%	2%	18%	0%	12%	4%	5%	0%
Cloxacillin	0%	0%	0%	1%	0%	0%	0%	0%	21%	29%
Piperacillin	0%	27%	0%	22%	9%	17%	0%	35%	2%	0%
Clindamycin	0%	0%	0%	0%	0%	0%	0%	0%	71%	73%
Cephalexin	74%	31%	62%	38%	64%	13%	68%	24%	48%	29%
Cefuroxime	96%	97%	66%	55%	91%	74%	76%	45%	61%	39%
Cefotaxime	82%	54%	19%	85%	82%	48%	18%	75%	0%	0%
Ceftazidime	37%	76%	75%	91%	36%	87%	71%	85%	2%	0%
Ceftriaxone	92%	89%	69%	90%	100%	61%	76%	89%	0%	0%
Cefazolin	22%	61%	22%	41%	9%	52%	24%	31%	0%	0%
Amikacin	51%	88%	7%	48%	64%	91%	9%	55%	0%	0%
Gentamicin	88%	95%	92%	51%	91%	100%	91%	56%	57%	46%
Doxycycline	3%	3%	84%	38%	0%	9%	85%	31%	16%	39%
Chloramphenicol	15%	0%	0%	0%	9%	0%	0%	0%	0%	5%
Co-Trimoxazole	88%	78%	89%	79%	64%	39%	94%	69%	59%	61%
Nalidixic acid	95%	93%	95%	85%	82%	87%	97%	76%	5%	0%
Ciprofloxacin	56%	83%	88%	69%	64%	78%	88%	82%	79%	63%
Co-amoxiclav	6%	4%	3%	3%						
Colistin	0%	31%	2%	2%	0%	17%	0%	7%	0%	0%
Meropenem	5%	5%	7%	73%	18%	26%	9%	80%	0%	0%
Nitrofurantoin	5%	0%	6%	19%	9%	0%	3%	16%	0%	0%
piperacillin + tazobactam	2%	18%	2%	15%	9%	17%	0%	15%	0%	0%
The table is according to SOP recommendation of antibiotic to microorganism type Pediatrics: patient from age 0-12 year (as mentioned in the SOP) Adult: patient from age 12 and more										

Susceptibility test depends on the minimum inhibitory concentration (MIC) techniques using the microbroth dilution method, while the microbiology laboratories under investigation uses the disk diffusion method. Thus, the results are not reliable and are considered invalid, yet they are issued and treatment decision may be taken based on such results. More importantly, colistin is tested against UTI isolates and not reserved for much more serious infections (e.g., septicemias or meningitis)

Despite the recommendation of doxycycline by the SOP in adults, laboratory technicians decreased the uses of doxycycline for adults from 84% to 38% in *Enterobacteriaceae* after SOP implementation. Amikacin, gentamicin, and ciprofloxacin were used all the time pre- and post-SOP implementation, to the recommended microorganism except gentamicin was used for not recommended microorganism like *Streptococcus* spp. It was used for adults 57% pre-SOP and 46% post implementing SOP.

Unfortunately, doxycycline was used in the susceptibility testing of isolates from pediatric category (3% in *Enterobacteriaceae* before and after SOP implementation and 9% in *Pseudomonas* after the implementation of the SOP) as noted in table (4.5).

It seems that microbiology laboratory staff are succeeding in adherence to the SOP recommendations but not fully. In fact, there are clear violations of the SOP. Failure to fully adhere to the SOP recommendation could be attributed to several factors, including, lack or irregular supply of antimicrobial disks, disposables, media and other lab materials. Other factors were discussed at the qualitative part of the research.

4.9 Questionnaire results

Specialty and job titles of questionnaires respondents, laboratory specialists constituted 60% of the interviewed personnel, department heads (33%) and 7% are laboratory technicians as shown in **Figure (4.8).**

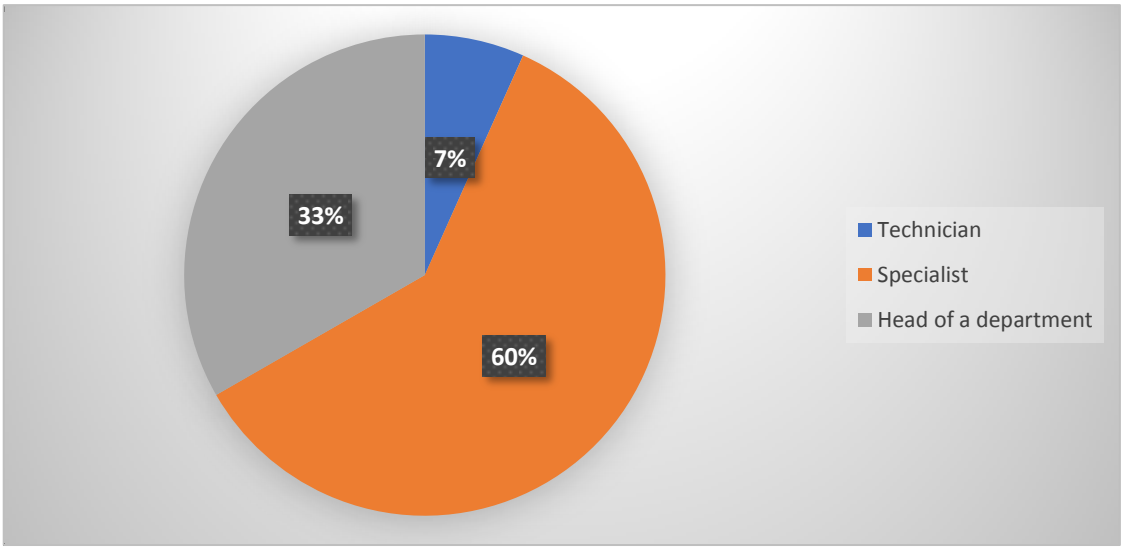


Figure (4.8) Distribution of respondents by job title

Figure (4.9) shows that about 73% believe that there are obstacles that delay implementing SOP but 27% disagree with them. Disagreement among respondents, may be influenced by their backgrounds, by the availability of laboratory materials and by the level of their motivation of applying the SOP.

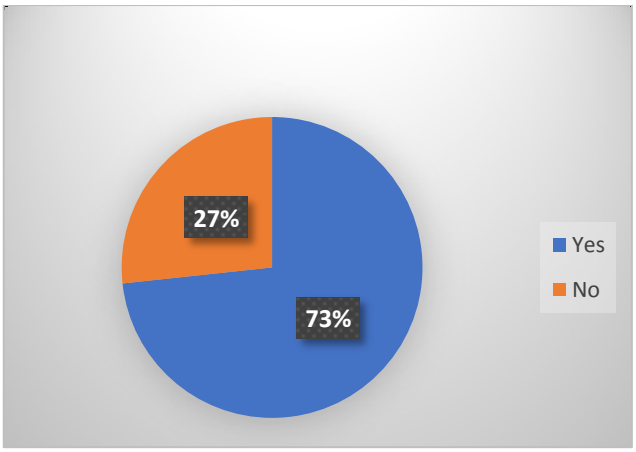


Figure (4.9) Are there any obstacles that delay the SOP implementation?

As shown in **Figure (4.10)**, 87% did not have any training by MoH and only 13% had training on SOP implementation.

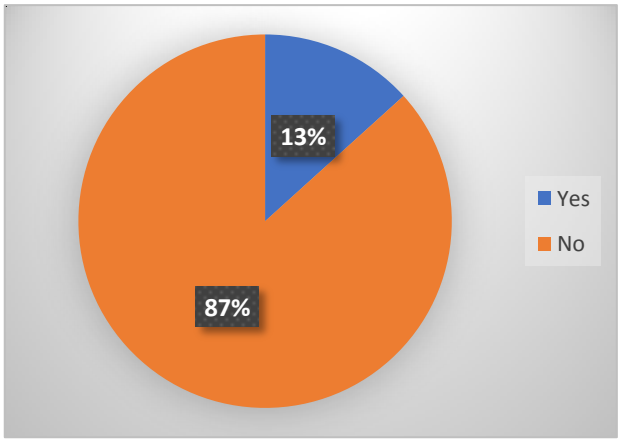


Figure (4.10) Did you have training on the SOP implementation

According to the questionnaire questions about the availability of a copy of SOP in their hands 93.3% of the answers were yes, but 6.7% of the answers were no in the **Figure (4.11).** and

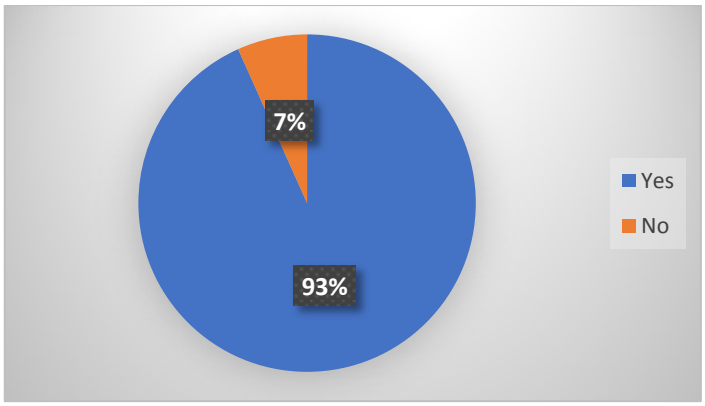


Figure (4.11) Do you have copies of SOP in your hand

Figure (4.12) shows that 66.6% has split copies of SOP while 33.3% don't have spilled copies.

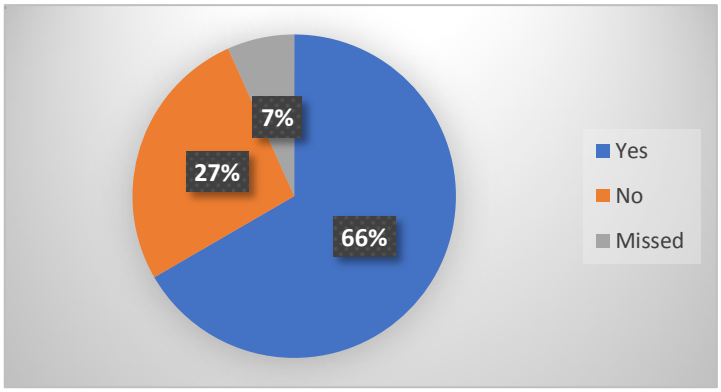


Figure (4.12) Do you have split SOP copies?

Figure (4.13) shows that 87% of the respondents read the whole content of the SOP while 13% of them did not, this predisposed to the next question in **Figure (4.14)** which is about the comment and criticism of the teamwork about the SOP If there are any notes any mistakes or defects which need editing, the answer was 46.7% yes while 53.3% was no.

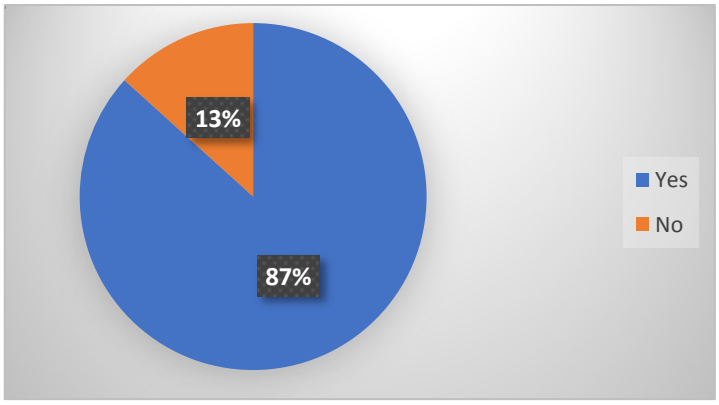


Figure (4.13) Did you read the whole content of the SOP?

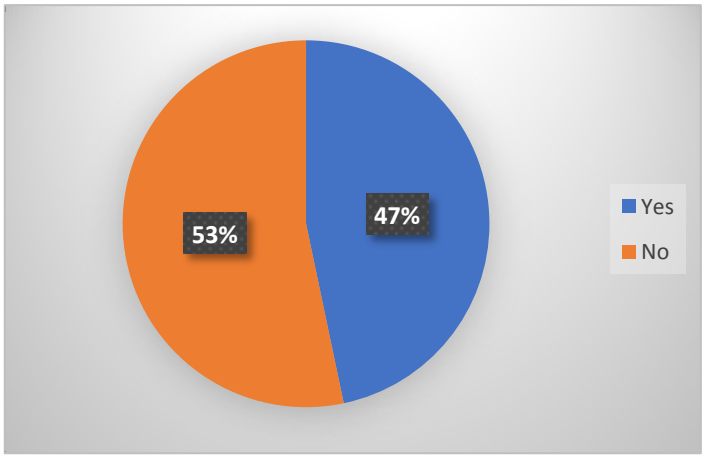


Figure (4.14): Did you note any errors that need to be corrected/revised?

Regarding the questionnaire, the answer to the question in **Figure (4.15)** about the impact of SOP on the culture result was 73.3% agreed. When asked about the nature of the impact (negative or positive); the answer was 0% for negative impact, 27% for no impact while 73% for positive. This shows that the SOP is useful from laboratory technicians' point of view.

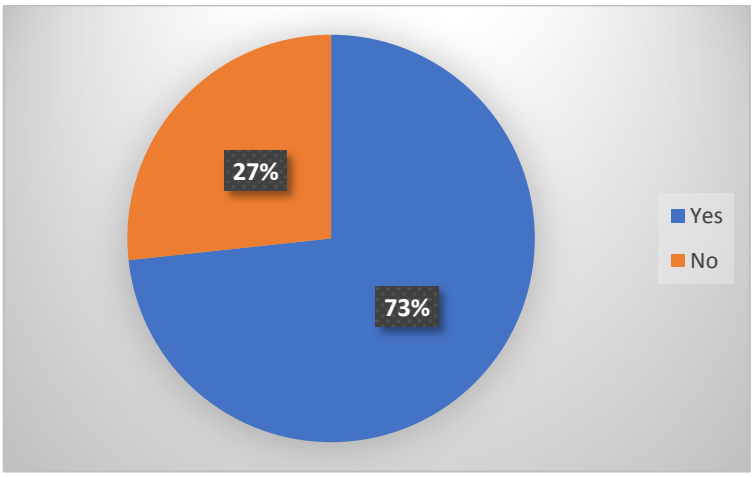


Figure (4.15) Did the SOP affected the culture results?

When we asked the respondents to questionnaire, if there is a positive impact of the SOP on the work or not, 87% said yes and 13% said no as shown in **Figure (4.16).**

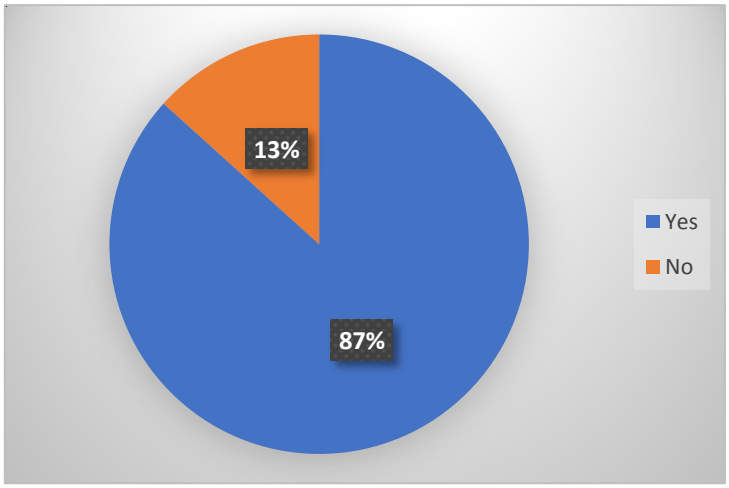


Figure (4.16) Respondents opinion on the positive impact of the SOP implementation

4.10 Interviews and focus groups result

During this research, this triangulation focused on the different dimensions (chapter 3), semi-structured questions around those dimensions were asked to the participants, to assess the intervention (the SOP implementation), and its impact.

4.10.1. The results of the interviews, focus groups and the questionnaire:

According to the opinion's interviewees that were conducted with key persons, specialists, and technicians, they answered the questions in-depth, few interviews were face to face and the others were by telephone (due to Coronavirus outbreak), those people were with diverse background and opinions.

4.10.2. Needs for the microbiology SOP:

According to the interviews and the focus groups analysis, the need to implement the SOP could be explained as the followings; before the SOP implementation, the microbiology procedures were not written and every technician/specialist was working based on his background and experience. Every laboratory has its procedure, and because the microbiology laboratories in these hospitals is fully manual and not automated (can`t be

controlled by calibration and control samples). In addition, there was no coordination, for these reasons, it was an urgent necessity to formulate and implement the SOP.

4.10.3. Level of SOP acceptance by the staff:

According to the interviews and focus groups, most of laboratory staff accepted the idea of adopting the SOP. This conclusion came out from the regular meetings and follow up of the SOP implementation and dissemination of updates. However, few of the staff did not accept it at first because it made some changes in the old method. Despite that, all laboratories are embracing the SOP and has high level of adherence.

The main recorded reason for acceptance is that it facilitated the work by documenting the sequence of steps that are needed to achieve the results.

4.10.4. The preparedness of the MoH to implement the SOP (logistics, staff, training, and facilities):

Despite the efforts made by the MoH in establishing this SOP which was reviewed several times, by professionals from inside and outside the MoH, it still needs other important logistics which are not available in the MoH laboratories. For instance, antimicrobial disks which may not be available or partially available and not all the time. Examples of necessary but not readily available materials mentioned by respondents are API20E and APINE (Biochemical identification system for bacterial isolates). Sometimes, laboratories depend on funded projects to compensate for the shortage of these important materials that are not available at MoH warehouse. The laboratories improvised connections among them to coordinate and compensate the shortage among themselves.

It is important to conduct on-site training on the SOP implementation for the laboratory technicians to ensure that everyone at the microbiology departments at all hospitals in MoH implements SOP have common understanding and skills. However, according to the

respondents' answers in **Figure (4.10)**, only 13% admitted that training took place. The MoH invited some of the microbiology staff to a workshop. However, the key informants answered that there were trainings and workshops. The conflicting answers may be due to the rotation of the laboratory technicians to various departments. Technicians who received training may be moved to other departments.

Shortage in laboratory staff constitutes a constant problem and has forced the head of the laboratory to assign laboratory technicians for chemistry or another department (less qualified to do microbiology work) to the microbiology laboratory to fill the gaps in the working schedule. This leads to change in the personnel all the time, the experience and the method varies from one to another which may have consequences on the variation in the method of practicing the SOP.

4.10.5. Problems and challenges tackled after implementing SOP:

The MoH has had some issues in the past, like the inaccuracy of the tests/results, unknown the level of resistance to the antibiotics from a specific microorganism, the experience of microbiology staff varied from one to another, also rotating laboratory technicians, that is the different methodology. Thus, the SOP was viewed as the proper way to overcome those issues. The SOP provided specific protocols to help unify and increases the skills of the microbiology staff.

According to respondents, the tests became more accurate and abiding to the recommended list of antimicrobials specific to tested microorganism. The SOP included information about every step. This detailed information contributed to making results valid and more reliable. The SOP helped the laboratory technician to avoid using unnecessary antimicrobials disks. In addition, the SOP facilitated the performance of laboratory technicians inside the laboratory by laying principles of every step inside the laboratory. It

is worth to mention, the SOP helped the less experienced lab technician to perform tasks easily.

The MoH confronted some problems like the accuracy of the tests, the level of resistance to the antibiotics from a specific microorganism was unknown, the experience is varied from one to another, also the moving of laboratory technicians for example from chemistry to microbiology makes him /her face a problem all the time, which is the different methodology, and the SOP was the proper way to solve this problem, the SOP posed a general protocol to help laboratory staff to work anywhere at the laboratory.

The tests became more accurate by using the specific antibiotics to the specific microorganism that is evidence-based written, the SOP provided the laboratory technician information about every step, this information is approved and written, results became valid and reliable, and the SOP helps the laboratory technician to avoid using a known resistant antibiotic to microorganism, besides, the SOP facilitates the work for laboratory technicians everywhere inside the laboratory by laying principles of every step inside the laboratory, also the SOP helped the inexpert to determine the type of antibiotic that will be used for a specific microorganism.

4.10.6. Errors and updates:

According to the interviews and the focus groups, one of the most important edits that were added by recommendations of the teamwork is adding the diameter of the susceptibility of the isolates to the antibiotic because of the huge variation between different antibiotics in the diameters of susceptibility test on petri dish.

Another editing that was writing mistakes like catalase-positive and catalase-negative.

4.10.7. The impact of SOP implementation on the results; is there a difference between pre- and post-implementing SOP?:

According to the interviews and the focus groups, the SOP reduced steps, made the laboratory technician more confident in their results, and drives the laboratory staff to work according to one protocol, and minimized the differences in techniques.

The SOP facilitated the process of identification of pathogens and the selection of suitable antimicrobials and unified the work in all laboratories. Improved reporting in all hospitals is one major advantage of the SOP. Another prominent advantage is rational antibiotic use according to spectrum and severity of infection. In addition, it eliminated all issues related to errors in determining the zoon of inhibition of growth.

The disadvantage of the SOP is the delaying of the result delivery in special circumstances; some cultures results may be multidrug-resistant, it takes more time if it is multidrug resistance, about 24 hours to repeat the test with other antibiotics, before the SOP the laboratory technicians were using all available antibiotics, so no need to repeat the test, but this make problem in many things, like specification in using antibiotics to a specific microorganism, also no need to waste all these antibiotics in all tests. But in normal cases, the SOP saves time because all the needed information to conduct the test is in hand and accessible, also using the most useful and less resistant, so the result will be effective and efficient.

4.10.8. The impact of SOP on patients, MoH, and community, Level of need to this intervention

As discussed previously, and according to the interview and the focus group answers, the SOP implementation saved time and effort. SOP is efficient and effective in most cases and tests. It guides the laboratory technician in determining the type of antimicrobials. The SOP is timesaving for the physicians and improved result reporting with data that are more

reliable to guide selecting proper antimicrobials therapy. This assists also in moving quickly from the empirical treatment to the culture-based treatment. On the other hand, it takes more time if the isolate is multidrug-resistant, it needs about 24 hours to repeat the test with other set of antimicrobials. Shorter turnover time, more reliable results and specific treatment surely will benefit patients. They will also help MoH to generate more reliable data about the level of antimicrobials resistance and thus better planning for reducing or avoiding multidrug resistance. This will also be reflected on both the local community and will add to the national and international efforts of combating antimicrobial resistance.

4.10.9. The role of laboratory administration in boosting SOP implementation

The role of the laboratory administration is to solve problems, facilitate duties, and coordinate to achieve the mission. Regarding to the questionnaire; 100% of the answers to the questions about the seriousness, and follow up of the implementation of SOP was (yes), the administration of the laboratory was serious and they follow up the SOP implementation.

According to the interviews and the focus group's answers, the laboratory administration played a pivotal role during the implementation of the SOP. The administration is the liaison between the laboratory technician and the SOP improving committee. They record the notes and the errors that are observed by the laboratory technicians and conduct periodical meetings and discuss these notes and receive the update. The administration validates the updated hard copy of the SOP at every laboratory in every governmental hospital and thus, facilitates the accessibility to the SOP.

One important point highlighted by the administration of the laboratories, is that laboratory technicians should abide by the list of antimicrobials as recommended by the SOP.

4.10.10. Impact of SOP on workflow and laboratory results.

After the approving of the SOP in all the government hospitals laboratories, laboratory technicians faced unexpected situations. For instance, physicians request laboratory technicians to use antimicrobials other than those written in the SOP and support their request by protocols and guidelines for patient's treatment, which are different from with SOP. Thus, there should be integration between laboratory guideline and treatment protocols. This is to avoid and conflict to encourage physicians to request and trust the microbiology tests conducted at the MoH laboratories.

Chapter Five
Conclusion and Recommendations

This study aimed at exploring the pattern of the resistance of uropathogens to the commonly used antimicrobials. Moreover, to assess the microbiology SOP implementation, advantages disadvantages, and the adherence of laboratory staff to the SOP.

In this chapter, the most prominent conclusions and recommendations are listed.

5.1 Conclusion

Uropathogens isolated from patients attending the four governmental hospitals included in this study, showed variation among species, hospitals, gender and age.

In light of the results of this study the following conclusion are drawn:

- Less than 25% of urine culture showed significant growth *in vitro*.
- *E. coli* (59.9%) and *Klebsiella* spp. (24.9%). are the main etiologic of the UTI in Gaza strip.
- The prevalence of the UTI in the female (71%) is higher than the prevalence in male (29%).
- Penicillin group is the least effective against the tested uropathogens.
- Amikacin and meropenem are the least resistant antimicrobials in most of the isolates
- Generally, *Klebsiella* spp. (53%) more resistant to antimicrobials than *E. coli* (45%).
- Isolates from pediatric hospitals are less resistant than adults' hospitals and Al-Shifa hospital is has the highest rates of resistance.
- In general, there is an explained correlation between the age of patients and the resistance to the antimicrobial.

- The resistance of *E. coli* and *klebsiella* spp.to antimicrobials in male is higher (53%, 57%) than in female (43%, 51%) respectively.
- There is a correlation between gender and age as independent variables and resistance of isolate to the antimicrobial as a dependent variable.
- The general resistance of *E. coli* and *Klebsiella* spp. to all of the used antimicrobials is close to 50%.
- The laboratory staff of the investigated MoH laboratories showed a limited adherence to the SOP instruction of using a specific antimicrobial to specific isolate.
- The SOP achieved many of the intended goals, e.g., written protocol for laboratory, regulate and unify the use of antimicrobials, saving time, timely access to the needed information to perform as task, and more importantly, standardizing the work methodology and results.
- In general, microbiology laboratory staff believed that the SOP has a positive impact on the patient, MoH, and community.
- There are still some issues that need to be resolved by the Laboratory administration to implement the SOP properly, like the shortage of logistics, manpower, and training.
- One attributed disadvantage of the SOP is the lack of integration with treatment protocols. Another prominent issue was the delays in results in case of MDR isolates.
- There are continues attempts by the laboratory administrations to improve the SOP, and solve the problems that prevent the SOP implementation through networking and NGO projects, and continuous meetings to review, update and improve the SOP.

5.2 Recommendations

- The establishment of an antimicrobial stewardship department by the Ministry of Health to monitor/control the use of antimicrobials is recommended.
- Antimicrobials should be regarded and dealt with as prescription drugs only and their use should be highly regulated and monitored.
- Penicillin group should not be used for the empirical treatment of UTIs because their resistance is closed to 100%.
- The higher laboratory administration should ensure the proper implementation SOP and increase the level of adherence.
- Coordination when establishing/reviewing treatment protocols and writing the SOP would greatly influence the adherence of laboratory staff to the antimicrobials listed in the treatment protocols.
- Periodical review of both the SOP and treatment protocols in light of the existing resistance data is highly recommended
- The laboratory administration of MoH should exert every effort to facilitate the SOP implementation by providing all the logistics to implement the SOP properly
- MoH should conduct training for the laboratory technicians to ensure proper and unified understanding.
- Physicians should minimize the empirical use of antimicrobials in non-life-threatening infection and rely more on culture and sensitivity for specific treatment.
- This type of study should be performed regularly to monitor the resistance of microorganisms to antimicrobials, not only for UTI but also for all types of infections for humans and animals as well.

5.3 Further studies

The following studies are recommended to:

- Attempt to better understand the correlation between gender and age and resistance of the isolates to antimicrobials.
- Determine the factors that contributed to the high resistance exhibited by Al-Shifa Hospital isolates.
- Large and continuous surveillance studies to monitor and evaluate multidrug resistance in the Gaza Strip.

5.4 Limitations of the study

- This research conducted during covid-19 pandemic which reduced the movement and face to face meetings and most of the interviews and focus groups and questionnaire responding was by telephone

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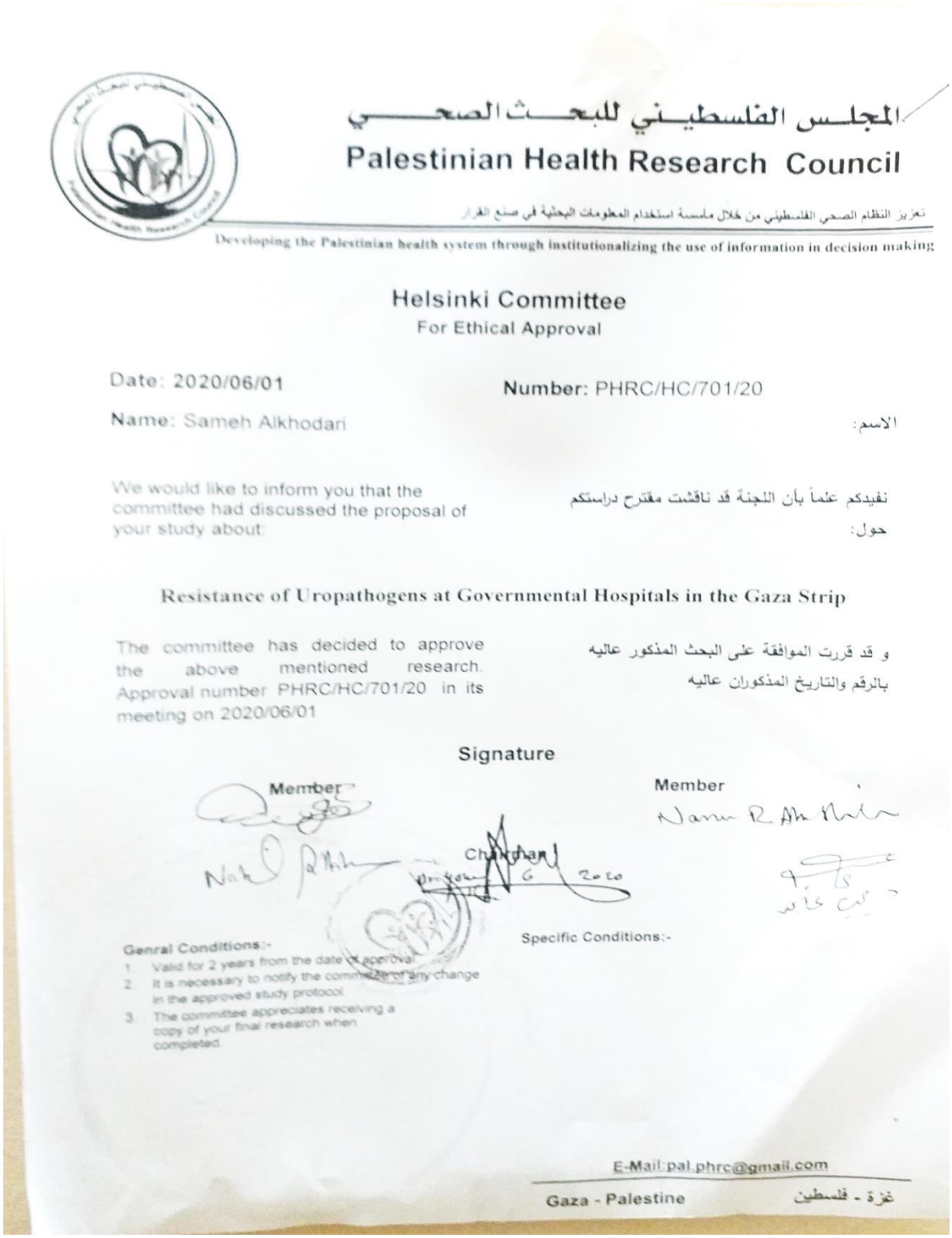
Annexes:

Annex 1: Helsinki approval



المجلس الفلسطيني للبحث الصحي

Palestinian Health Research Council

تعزيز النظام الصحي الفلسطيني من خلال مأسسة استخدام المعلومات البحثية في صنع القرار

Developing the Palestinian health system through institutionalizing the use of information in decision making

Helsinki Committee

For Ethical Approval

Date: 2020/06/01 Number: PHRC/HC/701/20

Name: Sameh Alkhodari الاسم:

We would like to inform you that the committee had discussed the proposal of your study about: نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:

Resistance of Uropathogens at Governmental Hospitals in the Gaza Strip

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/701/20 in its meeting on 2020/06/01 و قد قررت الموافقة على البحث المذكور عاليه بالرقم والتاريخ المذكوران عاليه

Signature

Member Member

Chairman

Genral Conditions:-

1. Valid for 2 years from the date of approval.
2. It is necessary to notify the committee of any change in the approved study protocol.
3. The committee appreciates receiving a copy of your final research when completed.

Specific Conditions:-

E-Mail:pal.phrc@gmail.com

Gaza - Palestine غزة - فلسطين

Annex 2: Researcher Mission Facilitation Form

State of Palestine
Ministry of health

دولة فلسطين
وزارة الصحة

التاريخ:13/04/2020
الرقم المتسلسل 1580 47

السيد : رامي عبد سليمان العبادلة المحترم

مدير عام بالوزارة /الإدارة العامة لتنمية القوى البشرية – /وزارة الصحة

السلام عليكم ,,,

الموضوع/ تسهيل مهمة الباحث// سامح الخضري

التفاصيل //
بخصوص الموضوع أعلاه، يرجى تسهيل مهمة الباحث/ سامح عطية الخضري
الملتحق ببرنامج ماجستير الصحة العامة – مسار علم الأوبئة – جامعة القدس أبوديس بغزة في إجراء بحث بعنوان:-
"Resistance of Uropathogens at Governmental Hospitals in the Gaza Strip"
حيث الباحث بحاجة لنتائج تحاليل المزارع البكتيرية التي أجريت للمرضى الذين يعانون من التهابات المسالك البولية في مستشفيات قطاع غزة (مجمع الشفاء الطبي – مستشفى غزة الأوربي – مستشفى النصر للأطفال – مستشفى الدرة)، إضافة للعينة استبانة من عدد من العاملين في المختبرات وعقد مقابلات معمقة ومجموعات بؤرية مع مدراء المختبرات في وزارة الصحة، بما لا يتعارض مع مصلحة العمل وضمن أخلاقيات البحث العلمي، ودون تحمل الوزارة أي أعباء أو مسئولية.
وتفضلوا بقبول التحية والتقدير,,,
ملاحظة / تسهيل المهمة الباحث بالدراسة أعلاه سالح لمدة 6 أشهر من تاريخه

محمد ابراهيم محمد السرساوي
مدير دائرة/الإدارة العامة لتنمية القوى البشرية –

التحويلات

- محمد ابراهيم محمد السرساوي(مدير دائرة) ← راضي عبد سليمان العبادلة(مدير عام بالوزارة) ← إجراءاتكم بالخصوص(13/04/2020)
- راضي عبد سليمان العبادلة(مدير عام بالوزارة) ← هاني سلطان ارميح الوحيدي(مدير وحدة) ← إجراءاتكم بالخصوص(13/04/2020)
- راضي عبد سليمان العبادلة(مدير عام بالوزارة) ← أيمن عبد الرحيم طه الحلبي(مدير عام بالوزارة) ← إجراءاتكم بالخصوص(13/04/2020)
- راضي عبد سليمان العبادلة(مدير عام بالوزارة) ← عبد السلام محمد عبد صباح(مدير عام بالوزارة) ← إجراءاتكم بالخصوص(13/04/2020)
- عبد السلام محمد عبد صباح(مدير عام بالوزارة) ← مصطفى سليم عبد الكحلوت(مدير مستشفى) ← إجراءاتكم بالخصوص(13/04/2020)
- عبد السلام محمد عبد صباح(مدير عام بالوزارة) ← محمد محمد عبد الحليم ابوسلمية(مدير مستشفى) ← إجراءاتكم بالخصوص(13/04/2020)
- عبد السلام محمد عبد صباح(مدير عام بالوزارة) ← يوسف فوزي اسماعيل العقاد(مدير مستشفى) ← إجراءاتكم بالخصوص(13/04/2020)

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Annex 3: Request to obtain data from the laboratories of MoH

التاريخ: 2019/10/22

الأستاذ عميد مشتهى المحترم

تحية طيبة وبعد

الموضوع: طلب مساعدة في الحصول على بيانات تخص درجة حساسة البكتيريا للمضادات الحيوية

بداية أثمن جهودكم في خدمة العلم والبحث العلمي وأود أن أعرفكم على نفسي

الاسم: سامح الخضري

الشهادة الجامعية: بكالوريوس صيدلة جامعة الازهر والان طالب ماجستير صحة عامة جامعة القدس

مكان العمل: مستشفى سمو الشيخ حمد بن خليفة آل ثاني للتأهيل والأطراف الصناعية

أرجو من سيادتكم مساعدتي في انجاز رسالة الماجستير التي هي بعنوان:

Resistance profiles of bacterial isolates at governmental hospitals in the Gaza Strip.

حيث أنه وبناء على اتصال هاتفي من خلال مشرفي على هذه الرسالة أ.د. عبد الرؤوف المناعمة مع د. محمد العبادلة ومع سيادتك وقد أبديتما مبدئيا موفقة سيادتكما بالنظر في أمر تسهيل مهمتي بالحصول على بيانات تعلق بالرسالة مذكورة بالمرفق.

مع العلم أن البيانات المطلوبة بعد الحصول على كافة الموافقات الرسمية من الجامعة ووزارة الصحة في الفترة من 2019/1/1 وحتى 2019/12/31 ولكم جزيل الشكر.

ملاحظة: مرفق بعض التفاصيل تخص الرسالة للتوضيح.

وتفضلوا بقبول فائق الاحترام والتقدير

الباحث: سامح الخضري

Annex 4: Data collection form MoH Hospitals

Sample NO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Date															
Lab															
Gender															
Age															
Ward															
Result															
Organism															
Penicillin G															
Ampicillin															
Amoxicillin															
Cloxacillin															
Piperacillin															
Erythromycin															
Clindamycin															
Cephalexin															
Cefuroxime															
Cefotaxime															
Ceftazidime															
Ceftriaxone															
Cefazolin															
Amikacin															
Gentamicin															
Tetracycline															
Doxycycline															
Chloramphenicol															
Co Trimoxazole															
Nalidixic acid															
Ciprofloxacin															
Aztreonam															
Rifampicin															
Vancomycin															
Rifamycin															
Azithromycin															
Co amoxiclav															
Colistin															
Meropenem															
Nitrofurantoin															
Piperacillin-Tazobactam															

Annex 5: Questionnaire

جامعة القدس كلية الصحة العامة علم الأوبئة يوليو /2020	

عنوان البحث:

Resistance of Uropathogens at Governmental Hospitals in the Gaza Strip

الزميل/ة المحترم/ة:

أتمنى منك المساعدة في تعبئة هذه الاستبانة والتي تهتم بالمقارنة بين نتائج المزارع في قسم الميكروبيولوجي قبل وبعد العمل بنظام Standard Operation Procedure (SOP)والذي تم تطبيقه ابتداء من تاريخ 2019/6/1.

مدة تعبئة الاستبيان لن تزيد عن 10 دقائق، ولك جزيل الشكر.

الباحث: سامح الخضري

المحور الأول: المعلومات الشخصية		رقم الاستبانة		
مكان العمل				
طبيعة العمل	☐فني	☐ أخصائي	☐ رئيس قسم	☐ مدير مختبر
عدد سنوات الخبرة				
عدد المستشفيات الحكومية التي عملت بها سابقا؟				
المحور الثاني: معلومات عن SOP				
هل يوجد لديكم نسخة في القسم SOPخاص بالميكروبيولوجي؟	☐ نعم	☐ لا		
هل هو مطبق؟	☐ نعم	☐ لا		
متى بدأ تطبيقه؟				
المحور الثالث: اتاحة المادة العلمية				
هل توجد منه نسخ بين أيديكم؟	☐ نعم	☐ لا		
هل توجد منه نسخ **مجزأة** بين أيديكم؟	☐ نعم	☐ لا		
كم عدد النسخ المتوفرة؟	( ) نسخة			
هل اطلعت على المحتوى كاملا؟	☐ نعم	☐ لا		
هل هناك أخطاء أو ملاحظات فيه ترغب في تعديلها في المستقبل؟	☐ نعم	☐ لا		
أذكر مثال:				
المحور الرابع: التدريب				

هل تم تدريبك على SOP؟		☐ نعم		☐ لا	
متى أجري آخر تدريب لك على SOP؟					
أثر التدريب؟	☐ سيئ جدا	☐ سيئ	☐ مقبول	☐ جيد	☐ ممتاز
أين تم تدريبكم؟		☐ في مختبركم		☐ في مكان آخر	
المحور الخامس: رأيك					
هل تعتقد أن SOPمفيد من حيث أثره على النتائج؟		☐ نعم		☐ لا	
وضح					
هل أثر على نتائج المزارع؟		☐ نعم		☐ لا	
وضح					
هل كان لتطبيق SOP نتيجة؟	☐ سلبية		☐ لا يوجد أثر		☐ إيجابية
وضح					
باعتقادك هل SOP يطبق بنفس الالية في كل مستشفيات الوزارة؟		☐ نعم		☐ لا	
وضح		☐ لا أعرف			
المحور السادس: تسهيل الإدارة للعمل من خلال SOP					
ما مدى جدية الإدارة في سعيها لتطبيق ال SOP في مختبركم؟					
هل توفر المواد اللازمة لتطبيق الSOP ؟		☐ نعم		☐ لا	
وضح					
هل تتابع الإدارة التنفيذ؟		☐ نعم		☐ لا	
وضح					
هل تراجع الإدارة النتائج وتتأكد من ملائمته وتتواصل مع الجهات المعنية للتعديل ان لزم الامر؟		☐ نعم		☐ لا	
وضح					
هل توجد أي عوامل تعيق العمل بنظام SOP؟		☐ نعم		☐ لا	
وضح					

Annex 6: ANOVA Scheffe test for age groups

Scheffe												
Dependent Variable			Mean Difference (I-J)	Std. Error	Sig.		Dependent Variable			Mean Difference	Std. Error	Sig.
Ampicillin	0-28 day	29d-1 year	-23.792	15.925	.530		Cefuroxime	0-28 day	29d-1 year	-11.609	11.920	.814
		1-12 y	-33.209	15.925	.237				1-12 y	-20.675	11.920	.398
		Adult	-55.115-*	15.925	.012				Adult	-40.743-*	11.920	.013
	29d-1 year	0-28 day	23.792	15.925	.530			29d-1 year	0-28 day	11.609	11.920	.814
		1-12 y	-9.416	15.925	.950				1-12 y	-9.066	11.920	.901
		Adult	-31.323	15.925	.286				Adult	-29.133	11.920	.125
	1-12 y	0-28 day	33.209	15.925	.237			1-12 y	0-28 day	20.675	11.920	.398
		29d-1 year	9.416	15.925	.950				29d-1 year	9.066	11.920	.901
		Adult	-21.907	15.925	.598				Adult	-20.068	11.920	.425
	Adult	0-28 day	55.115*	15.925	.012			Adult	0-28 day	40.743*	11.920	.013
		29d-1 year	31.323	15.925	.286				29d-1 year	29.133	11.920	.125
		1-12 y	21.907	15.925	.598				1-12 y	20.068	11.920	.425
Amoxicillin	0-28 day	29d-1 year	-17.314	14.860	.716		Cefotaxime	0-28 day	29d-1 year	-15.976	10.204	.490
		1-12 y	-52.382-*	14.860	.010				1-12 y	-10.149	10.204	.804
		Adult	-52.223-*	14.860	.010				Adult	-27.362	10.204	.077
	29d-1 year	0-28 day	17.314	14.860	.716			29d-1 year	0-28 day	15.976	10.204	.490
		1-12 y	-35.068	14.860	.147				1-12 y	5.827	10.204	.955
		Adult	-34.909	14.860	.150				Adult	-11.386	10.204	.743
	1-12 y	0-28 day	52.382*	14.860	.010			1-12 y	0-28 day	10.149	10.204	.804
		29d-1 year	35.068	14.860	.147				29d-1 year	-5.827	10.204	.955
		Adult	.159	14.860	1.000				Adult	-17.213	10.204	.423
	Adult	0-28 day	52.223*	14.860	.010			Adult	0-28 day	27.362	10.204	.077
		29d-1 year	34.909	14.860	.150				29d-1 year	11.386	10.204	.743
		1-12 y	-.159	14.860	1.000				1-12 y	17.213	10.204	.423
Piperacillin	0-28 day	29d-1 year	-18.316	12.193	.525		Ceftazidime	0-28 day	29d-1 year	-.785	10.095	1.000
		1-12 y	-27.867	12.193	.168				1-12 y	-16.924	10.095	.429
		Adult	-48.320-*	12.193	.003				Adult	-19.482	10.095	.303
	29d-1 year	0-28 day	18.316	12.193	.525			29d-1 year	0-28 day	.785	10.095	1.000
		1-12 y	-9.551	12.193	.893				1-12 y	-16.139	10.095	.471
		Adult	-30.004	12.193	.121				Adult	-18.697	10.095	.339
	1-12 y	0-28 day	27.867	12.193	.168			1-12 y	0-28 day	16.924	10.095	.429
		29d-1 year	9.551	12.193	.893				29d-1 year	16.139	10.095	.471
		Adult	-20.453	12.193	.428				Adult	-2.558	10.095	.996
	Adult	0-28 day	48.320*	12.193	.003			Adult	0-28 day	19.482	10.095	.303
		29d-1 year	30.004	12.193	.121				29d-1 year	18.697	10.095	.339
		1-12 y	20.453	12.193	.428				1-12 y	2.558	10.095	.996
Cephalexin	0-28 day	29d-1 year	-23.097	13.064	.381							
		1-12 y	-35.176	13.064	.075							
		Adult	-46.725-*	13.064	.009							
	29d-1 year	0-28 day	23.097	13.064	.381							
		1-12 y	-12.079	13.064	.836							
		Adult	-23.627	13.064	.360							
	1-12 y	0-28 day	35.176	13.064	.075							
		29d-1 year	12.079	13.064	.836							
		Adult	-11.549	13.064	.854							
	Adult	0-28 day	46.725*	13.064	.009							
		29d-1 year	23.627	13.064	.360							
		1-12 y	11.549	13.064	.854							

العنوان: مقاومة مسببات التهابات المسالك البولية في المستشفيات الحكومية في قطاع غزة.

إعداد الباحث: سامح عطية الخضري

إشراف: أ. د. عبد الرؤوف المناعمة

الملخص

يعتبر سوء استخدام مضادات الميكروبات والإفراط في استخدامها من الأسباب الرئيسية لمقاومة بكتيريا المسالك البولية. تشجع منظمة الصحة العالمية البلدان على تنفيذ برامج الإشراف على مضادات الميكروبات، من أجل الاستخدام المناسب للأدوية التي يمكن أن تقلل من مقاومة الأدوية بمرور الوقت. الهدف العام من هذه الدراسة هو تحديد مسببات حدوث الأمراض البولية، لاستكشاف نمط مقاومتها لمضادات الميكروبات واختبار الاختلاف بين الجنس والفئات العمرية والمستشفيات. بالإضافة إلى ذلك، قيمت الدراسة أثر تطبيق إجراءات التشغيل المعيارية للأحياء الدقيقة (SOP) ومستوى الالتزام من قبل مختبرات أربعة مستشفيات حكومية في قطاع غزة.

لقد فحصت الدراسة بأثر رجعي (من 2019/1/1 إلى 2019/12/31) 11890 سجل مزرعة بول من أقسام الأحياء الدقيقة في أربع مستشفيات في قطاع غزة (الأوروبي، الشفاء، النصر، والدرة). تم جدولة جميع البيانات وتحليلها. تم إجراء تحليل البيانات باستخدام الإصدار 22 من SPSS . تم إجراء الاختبارات الإحصائية ذات الأهمية. اختبار chi-square (X2) ، اختبار T المستقل، اختبار ANOVAأحادي الاتجاه، تمت مقارنة المتغيرات باستخدام الجدولة المتقاطعة. اعتبرت القيمة P≤ (.05) ذات دلالة إحصائية. تم إجراء ثلاث مجموعات بؤرية، وثلاثة مقابلات معمقة مع مدراء المختبرات، وسبع مقابلات فردية معمقة، وأجاب خمسة عشر من فنيي المختبرات على الاستبيان. كلهم من قسم الأحياء الدقيقة في المستشفيات الحكومية في قطاع غزة. تم استخدام سؤال شبه منظم حول تأثير ومستوى الالتزام بالمشاركين. تم بدء الدراسة بعد الحصول على إذن من لجنة هلسنكي.

أظهرت النتائج أن الإشريكية القولونية كانت أكثر مسببات الأمراض البولية شيوعا (59.9٪) تليها كليبسيلا (24.9%) في قطاع غزة. ان انتشار عدوى المسالك البولية عند الإناث أعلى من الذكور (71٪)، ومع ذلك، فإن مقاومة العزلات لمضادات الميكروبات أعلى عند الذكور. بالإضافة إلى ذلك، هناك مقاومة عامة متزايدة للعزلات ضد المضادات الحيوية مما يحد من خيارات العلاج التجريبي.

لم يعد البنسلين فعالاً لعلاج عدوى المسالك البولية لأن مقاومة الكائنات الحية الدقيقة لهذه المجموعة من المضادات الحيوية لا تقل عن 90٪. المقاومة ل أمبيسلين (92.4٪) وأموكسيسيلين (91.1٪)، يليه الكوتريموكسازول (68.2٪)، سيفاليكسين (64.9٪)، دوكسيسيكلين (61.9٪)، حمض

النالیدیکسیك (53.6٪)، سیفوروکسیم (53.0٪)، سیفترياکسون (48.9%) ، سیفتازیدیم (43.1٪)، سیبروفلوکساسین (36.9٪) ، جنتامیسین (25.8٪) ، أقل مقاومة بین العزلات کانت تجاه أمیکاسین (3٪) ومیروبینیم (8٪)

إن التزام العاملین في المختبرات بـ SOP مرتفع ولکنه لیس مثالیًا ویتطلب المتابعة من قبل الإدارة. علاوة على ذلك، لا یوجد تکامل بین بروتوکول الأطباء وإجراء التشغیل المعیاري للمختبر.

في الختام، تباینت مقاومة مسببات الأمراض البولیة من مستشفى إلى آخر، بین الجنس والفئات العمریة. العوامل التي تسهم في زیادة المقاومة بشکل عام ومستشفى الشفاء بشکل خاص یجب التحقیق فیها في دراسات أخرى. هناك حاجة لبرنامج الإشراف على مضادات المیکروبات لمنع تفاقم المشکلة، وتقلیل (MDR) في المجتمع، وتقلیل إساءة استخدام المضادات الحیویة حیث نقوم بتقلیل مدمني المخدرات لأن کلاهما یشکل نفس الخطر على مجتمع المریض، وکذلك احتیاجات SOP المزید من المتابعة والتکامل مع کافة الأقسام الأخرى.

کلمات مفتاحیة: مسببات الأمراض، مقاومة العزلات لمضادات المیکروبات، التهاب المسالك البولیة، قطاع غزة.