ANTIMICROBIAL RESISTANCE PATTERNS

IN A

PORT ELIZABETH HOSPITAL

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CONTENTS

ABSTRACT

Antibiotic resistance in clinical bacterial isolates remains an ongoing problem requiring continuous monitoring to effect some form of control. Comparative studies have not been previously reported for the Eastern Cape Region, South Africa and this study was undertaken to monitor resistance patterns in clinical isolates from Provincial Hospital, Port Elizabeth. Over the three year period 1989 to 1991, 9888 susceptibility results from isolates examined in the SAIMR pathology laboratory were analysed and collated using a stand-alone computer program. Resistance patterns for a range of nineteen antibiotics were collated for isolates from various sampling points within the hospital. Results were reported as resistance patterns in individually isolated species. Levels of resistance in each species were compared to those reported from South Africa and abroad, and changing patterns of resistance were noted within the three year period at the Provincial Hospital, Port Elizabeth.

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ABBREVIATIONS

Abbreviations used for antimicrobial agents and organisms on the graphs.

PEN	=	Penicillin
AMP	=	Ampicillin
PE/AP	=	Penicillin/Ampicillin
PIP	=	Piperacillin
CDL	=	Cefamandole
TET	=	Tetracycline
COT	=	Cotrimoxazole
ERY	=	Erythromycin
CLI	=	Clindamycin
FUC	=	Fucidin
GEN	=	Gentamicin
TOB	=	Tobramycin
AMI	=	Amikacin
FOZ	=	Cefoxitin
TAX	=	Cefotaxime
VAN	=	Vancomycin
IMI	=	Imipenem
TAZ	=	Ceftazidime
OFL	=	Ofloxacin

CIP	=	Ciprofloxacin
NOR	=	Norfloxacin
Aani	=	*Acinetobacter anitratus*
Eclo	=	*Enterobacter cloacae*
Ecol	=	*Escherichia coli*
Kaer	=	*Klebsiella aerogenes*
Pmir	=	*Proteus mirabilis*
Smar	=	*Serratia marcescens*
Paer	=	*Pseudomonas aeruginosa*
Xmal	=	*Xanthomonas maltophilia*

CHAPTER 1

1. INTRODUCTION

The use of antimicrobial agents has been described as the greatest intervention ever in population genetics. The selective pressures of antimicrobial agents have provoked the emergence of resistance to drugs among many previously susceptible bacteria of clinical significance. Antibiotic resistance is a worldwide problem especially in developing communities and hospitals. It limits the number of useful antimicrobial agents, places constraints on those which can be used and may cause the usage of more toxic and/or more expensive agents (van den Ende, 1989).

In the hospital setting, the effectiveness of antibiotic treatment may be seriously compromised by resistance that is either intrinsic to the hospital flora or develops during the course of therapy (Buirma & Horrevorts, 1991). *In vitro* antimicrobial susceptibility tests provide useful information to direct clinicians in their choice of antibiotics for treatment of infections. Such tests can also be used to generate antibiograms that serve as tools for selecting antimicrobial agents to treat infection caused by identified pathogens prior to the availability of the susceptibility test reports for those pathogens (Jenkins, 1992). Therefore, antimicrobial susceptibility patterns are of great importance in a hospital environment as medical staff often need to treat life-threatening situations empirically i.e. before antimicrobial test results are available.

The high cost of empiric therapy, usually an extended spectrum new β-lactam agent combined with an aminoglyoside, should encourage more rational use of more specific, less costly, and potentially less toxic antibiotics based on the isolation, identification and susceptibility test results provided by the microbiology laboratory. The laboratory in turn should also keep the medical staff abreast of changes in antimicrobial susceptibility patterns (Washington, 1984).

Approximately one third of patients admitted to hospitals receive antimicrobial drugs. Such antibiotic use causes coincidental changes in the flora of individual patients and in the hospital locale. These changes have an important influence on the prevalence and character of nosocomial infections. The frequency of emergence of antibiotic-resistant organisms within a hospital or ward varies from place to place and is proportional to the degree of use of the specific antimicrobial drugs tested (Daschner & Borneff, 1977).

Restrictions on the use of certain antibiotics may be recommended in some hospitals, but have little effect on the prevalence of nosocomial infections and the purpose is to minimise the problem of antibiotic resistance and favourably influence the treatment of those infections that occur.

Each Provincial Hospital has an antibiotic policy, often slightly different from other hospitals, and the only assistance the doctors have available to them regarding resistance, is what they glean from the laboratory reports and the information published quarterly by the Antibiotic Study Group of South Africa (A.S.G.S.A.) in The South African Medical Journal. This data consists of the number of isolations and the incidence of

antibiotic resistance from seven academic training hospitals in South Africa from cerebrospinal fluid and blood cultures. As Port Elizabeth does not fall in this category, this information is of little help to the local doctors. Each hospital needs to have access to its own resistance data as this does vary from hospital to hospital and indeed between different sections of the same hospital (Friedland, 1990). Because of this fact very little information is published because it is considered of little consequence to other hospitals.

Thus, an understanding of the epidemiology of resistant species and resistance patterns and a knowledge of those combinations of drugs and microbes with a high probability of developing resistance are critical for the clinician in choosing appropriate antimicrobial regimens. Such an understanding can be achieved through surveillance studies (Buirma & Horrevorts, 1991). Appeals from clinicians have appeared in the literature for more specific data covering (i) a comparison of antimicrobial sensitivities in different hospitals and in different sections of each hospital especially high-care areas, (ii) the changes in sensitivity patterns with changes in antibiotic policy and with time, and (iii) sensitivity patterns to antibiotics such as amikacin and the newer antibiotics e.g. ciprofloxacin and imipenem (Friedland, 1990).

The following micro-organisms have been isolated the most frequently in the Provincial Hospital Port Elizabeth (PHPE) and are cited as the most common nosocomial pathogens in the literature (Crowley & Edwards, 1986; Smith & Eng, 1989). The aim of this study is thus to examine the antibiotic resistance patterns of these organisms in PHPE.

GRAM-POSITIVE COCCI:

Staphylococcus aureus including Methicillin resistant strains (MRSA).

Staphylococcus epidermidis including Methicillin resistant strains (MRSE).

Enterococcus faecalis.

Enterococcus faecium.

GRAM-NEGATIVE BACILLI:

Acinetobacter anitratus.

Enterobacter cloacae.

Escherichia coli

Klebsiella aerogenes.

Proteus mirabilis.

Pseudomonas aeruginosa.

Serratia marcescens.

Xanthomonas maltophilia.

1.1. GRAM-POSITIVE COCCI

During the early 1980's a resurgence of Gram-positive cocci causing severe infection was noted (McGowan, 1988). Much of this increase was closely associated with the development of antimicrobial resistance in several genera.

The Centres for Disease Control (CDC) in the U.S.A. initiated a national surveillance programme for hospital infection, the National Nosocomial Infections Study (N.N.I.S.)

and in 1984, three groups of Gram-positive cocci, *S. aureus*, *S. epidermidis* and Group D *Streptococci*, were found to account for 34% of all bloodstream pathogens (Horan *et al.*, 1986).

Staphylococci are members of the Micrococcaceae family which includes two genera: the micrococci and the staphylococci. The staphylococci in turn, have 3 clinically important species: *S. aureus*, *S. epidermidis* and *S. saprophyticus* (Pfaller & Herwaldt, 1988; Sheagren, 1984). They are non-motile, non-sporeforming, gram-positive, facultatively anaerobic, clustering cocci that produce catalase (Pfaller & Herwaldt, 1988). *S. aureus* continues to be a pathogen of major importance. The organism has developed mechanisms of circumventing almost every attempt to control it, either by host's defences or by newer antibiotic agents (Brumfitt & Hamilton, 1989; Sheagren, 1984).

Staphylococci are still the most common agents implicated in hospital-acquired infections. In addition to *S. aureus*, *S. epidermidis* has attracted widespread interest, since these two species have emerged as the most frequent pathogens in foreign-body related infections. The emergence of MRSA has resulted in increasing use of potentially toxic and extremely expensive antibiotics (Kappstein & Daschner, 1991).

1.1.1. *STAPHYLOCOCCUS AUREUS*

Historically *S. aureus* has been recognised as one of the most devastating human pathogens. Initially, the organism proved to be susceptible to the earliest antimicrobial substances, the sulphonamides and penicillin (Sheagren, 1984). However, as antibiotic

use increased through the 1950's, resistance rapidly developed (Brumfitt & Hamilton, 1989; Shanson, 1981; Sheagren, 1984).

Tetracyclines were increasingly used during the 1950's and by the late 1950's, outbreaks of infections occurred due to penicillin- and tetracycline-resistant *S. aureus* strains. Erythromycin was widely used to treat these infections and soon resistance emerged to this agent, rapidly in some hospitals but only after many months in others (Shanson, 1981).

In the mid and late 1960's multiple antibiotic-resistant strains of *S. aureus* continued to cause frequent outbreaks of hospital infection. However, there was a gradual general decline in multiple antibiotic resistance compared with the late 1950's and early 1960's throughout the world. A major change during the 1960's included the introduction of methicillin which was penicillinase stable (Shanson, 1981).

In the 1970's and 1980's MRSA strains emerged. By 1986 MRSA strains accounted for 10% of *S. aureus* in large teaching hospitals, 6% in non-teaching hospitals and 4,6% in small teaching hospitals in the U.S.A. (McGowan, 1988).

Historically, *S. aureus* has gained increased resistance to antibiotics (Brumfitt & Hamilton, 1989). This organism has shown itself to be a remarkably versatile pathogen capable of causing a range of infections more diverse than most other bacterial genera. It has maintained its role as one of the commonest human pathogens at various sites in both community-acquired and hospital-acquired infection (Eykyn, 1988). *S. aureus* has

become a major clinical pathogen and a leading cause of nosocomial infections (Liu & Buescher, 1990; van den Ende, 1989).

Bauer *et al.* (1960) found that about 80% of *S. aureus* were resistant to penicillin and that erythromycin resistance gradually increased from 14% to 31% over the 5 year period, 1955 - 1959.

In their review Dagan *et al.* (1992) reported that during the last decade, the sensitivity to erythromycin of *S. aureus* strains isolated from impetigo was ± 90% or higher. Recently however, erythromycin resistance rates of 32% and 48% were reported from Israel and Australia respectively. This change together with evidence of resistance to penicillin and erythromycin in their region prompted the reviewers to undertake a prospective study. They found that 28% of *S. aureus* strains were resistant to erythromycin.

In a multicentre study conducted by the Paul Ehrlich Society, *S. aureus* strains isolated from West Germany, Austria and Switzerland were tested against 12 antibiotics between 1976 and 1982. They found a significant difference in the number of susceptible strains between the different centres (Table 1.1.) and were unable to demonstrate significant changes from 1976 to 1982 for any antibiotic (Wiedemann & Kresken, 1984).

Table 1.1. Percentage of susceptible *S. aureus* strains from different European laboratories (Wiedemann & Kresken, 1984).

	Lubeck	Bonn	Berlin	Munich	Vienna	Zurich
Penicillin	28,2	25,8	34,0	33,0	13,0	26,1
Oxacillin	99,0	99,7	98,8	99,1	82,1	98,7
Gentamicin	93,2	94,0	80,9	93,9	49,6	96,2
Tetracycline	79,6	87,3	72,2	82,6	43,1	72,6
Erythromycin	81,9	92,0	74,5	89,6	44,7	73,2
Lincomycin	99.0	98,8	99,4	100	96,7	99,4
Cotrimoxazole	86,7	92,3	75,3	83,5	46,3	72,6

The sensitivity pattern to different antibacterial agents of *S. aureus* from the hospital personnel in a Nigerian hospital were reported as resistant to penicillin 95%, methicillin 0%, tetracycline 57,6%, cotrimoxazole 10,1% and gentamicin 8,6% (Olusanya & Ogeunledun, 1991).

In South Africa, data obtained in 1987 from A.S.G.S.A. centres showed *S. aureus* to be the most common blood culture isolated overall, of which 41,7% (range 23,5 - 66,3%) were MRSA (van den Ende, 1989).

In 1987 at the King Edward Hospital, Durban resistance rates for 413 blood culture isolates of *S. aureus* were: methicillin 29%, tetracycline 24%, erythromycin 17%, cotrimoxazole 14%, gentamicin 16%, clindamycin 1%, fusidic acid 0% and vancomycin 0% (van den Ende, 1989).

1.1.2. METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS*

MRSA strains were detected in the U.K. in 1960 soon after methicillin became available (Duckworth & Lothian, 1988; Eykyn, 1988; Shanson, 1981).

In the late 1970's, outbreaks of gentamicin-resistant methicillin-sensitive *S. aureus* and gentamicin-resistant MRSA were reported (Casewell, 1986; Eykyn, 1988). During the 1980's there was a sharp increase in the outbreaks of methicillin resistance in many parts of the world; U.K., Eire, U.S.A., Australia and South Africa (Casewell, 1986; Eykyn, 1988; Faoagali *et al.*, 1992). These epidemic strains are generally resistant to most anti-staphylococcal agents except vancomycin (Eykyn, 1988). They have been termed epidemic MRSA (EMRSA) because of their remarkable ability to spread within hospitals; some affected hospitals have reported up to 40% of their clinical isolates of *S. aureus* as MRSA (Eykyn, 1988; Shanson, 1981). Eykyn (1988) listed the main antibiotic sensitivities of *S. aureus* and *S. epidermidis* from patients in St Thomas Hospital, London (Table 1.2.).

Table 1.2. Percentage resistance of *S. aureus* and *S. epidermidis* hospital acquired isolates from bacteraemic patients (Eykyn, 1988).

Resistant to	S. aureus	S. epidermidis
Penicillin	88%	91%
Methicillin	3%	43%
Gentamicin	5%	51%
Fusidic Acid	2%	21%
Erythromycin	8%	36%

In the U.S.A. in the 1980's MRSA increased in all types of hospitals and was widespread throughout the country, the first report of an outbreak in the U.S.A. having come from Boston in 1968 (Brumfitt & Hamilton, 1989; McGowan, 1988). Ndawula *et al.* (1991) reported an outbreak of MRSA that showed resistance to cefuroxime, cefotaxime, piperacillin, ceftazidime, erythromycin and gentamicin, and sensitivity to fusidic acid, ciprofloxacin, tetracycline and vancomycin. Maple *et al.* (1989) determined antibiotic resistance patterns for 106 strains of MRSA from 21 countries. Twelve of the 15 highly multiresistant strains (resistant to either thirteen or fourteen agents) came from France, Turkey and Brazil. Resistance to the aminoglycosides and erythromycin was recorded in more than 90% of the isolates. All strains were sensitive to vancomycin. Resistance to other agents was as follows: tetracycline 86%, clindamycin 66%, fusidic acid 12%, ciprofloxacin 17%. Mulligan *et al.* (1988) found that there was an apparent acquisition over time of resistance to cotrimoxazole and gentamicin by endemic strains of oxacillin-resistant *S. aureus*.

Infections caused by MRSA stains are a serious medical problem because only a few effective therapeutic agents are clinically available (Brumfitt & Hamilton, 1989; Faoagoli *et al.*, 1992; Harnett *et al.*, 1991; Nakanishi *et al.*, 1991; van den Ende & Rotter, 1986). In New York City, 5,2% of *S. aureus* strains were quinolone resistant of which 93,9% were resistant to methicillin (Schaefler, 1989). In an Acute-Care Teaching Hospital, New York, ciprofloxacin-resistant MRSA isolates increased from ± 10% to 92,3% after 11 months of ciprofloxacin usage. Methicillin sensitive isolates remained uniformly susceptible 98,4% (Raviglione *et al.*, 1990). In another hospital the prevalence of quinolone resistance increased from 15 to 48% during a 6 month period. In Israel it

was noted that following the introduction of routine tests for quinolone susceptibility in August 1987, most clinical isolates of *S. aureus* were resistant to both methicillin and quinolones (Shalit *et al.*, 1989). In Canada, Harnett *et al.* (1991) found that 49% of the MRSA isolates were resistant to ciprofloxacin, 98% resistant to tobramycin, and 42% to gentamicin. Daum *et al.* (1990) demonstrated a marked emergence of resistance to ciprofloxacin among *S. aureus*. From 1984 to 1985 all isolates were susceptible to ciprofloxacin regardless of whether they were methicillin resistant or susceptible. Isolates of MRSA from 1989 showed a significant increase in resistance to ciprofloxacin; 55,1% of MRSA isolates and 2,5% of *S. aureus* (methicillin sensitive strains) were resistant to ciprofloxacin.

1.1.3. *STAPHYLOCOCCUS EPIDERMIDIS*

The coagulase negative staphylococci, with the exception of the urinary pathogen *S. saprophyticus*, are secondary pathogens - opportunists, rarely able to cause infections without the assistance of prostheses or intravascular or other catheters (Eykyn, 1988). These staphylococci were long regarded only as laboratory contaminants, which of course they still sometimes are (Pfaller & Herwaldt, 1988; Sheagren, 1984). Most routine laboratories use the nomenclature *S. epidermidis*, conveniently if inaccurately, to encompass all coagulase-negative staphylococci other than *S. saprophyticus* (Eykyn, 1988). In this thesis the name *S. epidermidis* will be used.

Coagulase-negative staphylococci have become formidable nosocomial pathogens and are the leading cause of nosocomial bacteraemia in the U.S.A., a situation due in large part

to their propensity for infecting in-dwelling intravascular devices (Archer, 1988; Pfaller & Herwaldt, 1988). Some strains produce a viscous extracellular substance or slime which enhances adherence to prosthetic devices. A major determinant of both the prevalence of these organisms in hospitals and the virulence of the infections they cause is their resistance to multiple antimicrobial agents (Archer, 1988)

The incidence of infection caused by *S. epidermidis* has increased strikingly over the past few years and in some types of hospital-acquired infection they are as common a pathogen as *S. aureus*. Furthermore, they are much more likely than *S. aureus* to be multiresistant (Eykyn, 1988; McGowan 1988). It has been shown that *S. epidermidis* may serve as the reservoir for transfer of resistance to *S. aureus* (Archer, 1988; McGowan 1988). The multiresistant phenotype can be defined as one that encompasses resistance to methicillin and at least 3 other unrelated classes of antibiotics (Archer, 1988). Coagulase-negative staphylococci are overall more resistant to antibiotics than *S. aureus* (Davies *et al.*, 1986; van den Ende, 1989).

1.1.4. *ENTEROCOCCUS SPECIES*

These organisms, primarily *E. faecalis* and *E. faecium*, are now the third most common organisms found in nosocomial infections and have a remarkable number of both intrinsic and acquired resistances (George, 1989; Gray *et al.*, 1991; Murray, 1990). In the N.N.I.S report of 1984 (Horan *et al.*, 1986), enterococci were the third most frequent source of nosocomial urinary tract infection and the sixth most frequent organisms in nosocomial bacteraemia. Resistant enterococci were encountered between mid - 1970's

and mid - 1980's in the U.S.A. (McGowan, 1988). The resistant strains have appeared most often in areas where antimicrobial use is high, such as that of intensive care (Bingen *et al.*, 1991; Gray *et al.*, 1991; McGowan, 1988; Oster *et al.*, 1990). Emerging drug resistance and increasing clinical significance of enterococcal isolates have created a need for accurate identification of species and surveillance of resistance patterns within this group (Bryce *et al.*, 1991).

Most strains of enterococci are relatively resistant to penicillin and ampicillin, *E. faecium* more so than *E. faecalis* (George & Uttley, 1989; Sapico *et al.*, 1989). Bryce *et al.* (1991), tested 140 strains of enterococci and found that high-level gentamicin resistance was seen in 12,1% of isolates. None of the isolates were vancomycin resistant and ampicillin resistance was 2,9%. These isolates were identified as *E. faecium*. In the United Kingdom in 1991 ampicillin resistance was not found in *E. faecalis* isolates. However, of *E. faecium* isolates 63,2% were resistant to ampicillin. The overall ampicillin resistance rate in enterococci in the hospital was 10,6% (Gray *et al.*, 1991). In California, Oster *et al.* (1990) found that 9,0% of all clinical enterococcal isolates were resistant to ampicillin.

Vancomycin has been successfully used as a single therapeutic agent against the enterococci and has shown good activity. Since the mid - 1980's, however, the development of resistance has become an increasing problem (Bingen *et al.*, 1991; Guiot *et al.*, 1991; Uttley *et al.*, 1989).

1.2. GRAM-NEGATIVE BACILLI

The family Enterobacteriaceae comprises numerous inter-related genera all of which are Gram-negative bacilli and microscopically indistinguishable. Other Gram-negative bacilli included in this study are *A. anitratus*, *P. aeruginosa*, and *X. maltophilia*.

Gram-negative bacilli (GNB) are common causes of hospital acquired infections especially in patients admitted to intensive care units (ICU).

1.2.1. *ACINETOBACTER ANITRATUS*

A. anitratus is an oxidase-negative, gram-negative cocco-bacillus often found in moist areas of the skin such as the groin, axilla, and the webbing of the toes. Widely prevalent in nature, the organism is considered to be a human commensal but can also be an important cause of nosocomial infections. Acinetobacter species are often resistant to multiple antimicrobial agents (Lambert *et al.*, 1990; Le Maistre *et al.*, 1985)

1.2.2. *ENTEROBACTER CLOACAE*

E. cloacae is increasingly recognised as an important pathogen and has been implicated in many episodes of hospital acquired infections, involving a high incidence of multiresistance (Gaston, 1988; John *et al.*, 1982; The Greek Society for Microbiology, 1989).

1.2.3. *ESCHERICHIA COLI*

E. coli has remained the most frequently isolated nosocomial pathogen in U.S. hospitals accounting for approximately 18,6% of hospital-acquired infections (Crowley *et al.*, 1986).

1.2.4. *PSEUDOMONAS AERUGINOSA*

P. aeruginosa is a particularly problematic pathogen and is a major cause of nosocomial infections (Korvick & Yu, 1991; Morrison & Wenzel, 1984). It is also the pathogen most responsible for morbidity and mortality in patients with cystic fibrosis. Mortality rates for *P. aeruginosa* bacteraemia ranged from 79 - 96% in the 1950's. Colistin, released in 1959, was the first antimicrobial agent with significant *in vitro* activity against *P. aeruginosa*. However, therapeutic efficacy failed to match *in vitro* susceptibility, and colistin was replaced by gentamicin and carbenicillin in the 1960's. A mortality rate of 71% was still found for bacteraemic patients treated with gentamicin and before long resistance to carbenicillin emerged. The pharmaceutical industry responded with a host of anti-pseudomonal agents eg.: ceftazidime, piperacillin, imipenem and ciprofloxacin (Korvick & Yu, 1991).

Bosso *et al.* (1989) evaluated and monitored susceptibility patterns of *P. aeruginosa* isolates collected from a cystic fibrosis (CF) population to ciprofloxacin, aztreonam and ceftazidime and seven other anti-pseudomonal agents, before use, during the early stages of use, and later after introduction of the three new antibiotics. They also studied concomitant resistance patterns among these ten agents during those same time periods.

Ciprofloxacin, piperacillin, ceftazidime and tobramycin showed decreases in susceptibility of 9,5%; 6,4%; 14,3% and 12,2% respectively. Gentamicin remained stable and amikacin showed an increase in susceptibility over the time period. Ciprofloxacin and ceftazidime were the newly introduced antibiotics. The decline in the rate of susceptibility to ceftazidime (14,3% resistant) could reflect the extensive use of this agent in their CF patients. Concomitant resistance within and among antibiotic classes was common.

1.2.5. *SERRATIA MARCESCENS*

S. marcescens has easily acquired resistance to many antibiotics and has been recognised as an important nosocomial pathogen (Fujimaki *et al.*, 1989).

1.2.6. *XANTHOMONAS MALTOPHILIA*

X. maltophilia is an important cause of nosocomial infections, especially in immunocompromised patients. Although cotrimoxazole remains the drug of choice, a significant number of patients are unable to tolerate this agent. The organism is isolated from a wide variety of clinical sources, including blood, the respiratory tract, urine, wounds and spinal fluid and from environmental sources eg. hospital water supplies, faucets, sinks, drains, respiratory and disinfectant solutions (Khardori *et al.*, 1990).

Aminoglycoside resistance is a major problem in South Africa. Although rates vary between centres, all have problems. In 1987, the A.S.G.S.A. reported gentamicin resistance figures in Blood Culture isolates (Table 1.3.) (van den Ende, 1989).

Table 1.3. Percentage resistance of South African isolates from Blood Cultures to gentamicin (van den Ende, 1989).

Organism	% Resistance	Range		
E. coli	4,1%	1,9	-	22,0%
Klebsiella spp.	30,3%	18,5	-	44,3%
Enterobacter spp.	15,3%	1,7	-	44,4%
P. aeruginosa	35,2%	11,1	-	42,1%

Van den Ende & Rotter (1986) analysed data on blood culture isolates for 1983 and January - July 1984 that has been reported by the A.S.G.S.A. and found disturbingly high resistance to gentamicin among Gram-negative bacilli. Over 30% of total isolates of Klebsiella spp. were resistant. In Pretoria and Bloemfontein over 10% of *E. coli* isolates were resistant. The overall prevalence of gentamicin resistance to Enterobacter spp. and Pseudomonas spp. was 6 - 8% and ± 25% respectively. Gentamicin is the aminoglycoside antibiotic most widely used in S.A. in the therapy of serious infections caused by GNB and has therefore been used as an indicator antibiotic for this group.

In the academic hospitals in the Johannesburg area the overall amikacin resistance in Gram-negative bacilli is ± 5%; at Hillbrow Hospital it is 5,5% and at Baragwanath Hospital 5,0%. In some of the ICU's the resistance is much higher i.e. in the Neonatal ICU at Baragwanath it is 13%. Eighteen percent of the isolates from pus specimens at

the Johannesburg Hospital are resistant to amikacin (Liebowitz & Koornhof, 1990). The bacteria isolated in hospitals that demonstrate this resistance are predominantly Acinetobacter, Pseudomonas and Klebsiella species. The authors reported that their findings were in contrast to those reported by Hesseling *et al.* (1989) from Tygerberg Hospital. Their study showed virtually no increase in amikacin resistance after almost exclusive use in the medical paediatric wards for an 18 month period (Hesseling & van der Merwe, 1989).

In Pakistan it was found that there was a high incidence of drug resistance to ampicillin and gentamicin among GNB (mean = 67%) in the neonatal unit at Aga Khan University Hospital (Karachi). A condensed summary of the percent of resistant strains to commonly used antibiotics is given in Table 1.4. (Bhutta *et al.*, 1991).

Table 1.4. Antibiotic resistance pattern of common organisms isolated in Pakistan. The figures indicate the percentage of resistant strains (Bhutta et al., 1991).

	No. of Isolates	Gentamicin	Amikacin	Ampicillin	Cefoxitin
E. coli	8	43%	29%	86%	14%
Klebsiella spp.	17	59%	6%	100%	24%
Enterobacter spp.	3	33%	0%	33%	0%
Serratia spp.	4	100%	0%	100%	0%
Pseudomonas spp.	7	43%	14%	86%	43%

In Riyadh, the capital of the Kingdom of Saudi Arabia, a survey was undertaken to determine the prevalence of gentamicin resistance. Table 1.5. contains a summary of their results (Moaz *et al.*, 1989).

Table 1.5. Percentage of gentamicin resistance in Riyadh, Saudi Arabia (Moaz et al., 1989).

	% of Resistance to Gentamicin
E. coli	1,6
Klebsiella spp.	8,6
Ent. cloacae	9,3
Serratia spp.	20,7
Proteus mirabilis	15,0
Acinetobacter spp	37,2
Ps. aeruginosa	26,6

Previous studies in Riyadh in 1978 and 1983 showed no gentamicin resistance in *E. coli* or *Klebsiella spp.* and a level of 1,6% in *P. mirabilis* isolates.

In 1983 and 1984 a survey of resistance of *P. aeruginosa* to aminoglycosides and β-lactam antibiotics was conducted in the Netherlands. Ten percent of the isolates were resistant to gentamicin. Although tobramycin was slightly more active than gentamicin, cross-resistance was nearly complete. Nearly all the gentamicin-resistant strains were susceptible to amikacin. Nine percent of the isolates were resistant to carbenicillin and 0,6% to ceftazidime (Neeling *et al.*, 1987).

1.3. INTENSIVE CARE

Intensive Care Unit (ICU) patients represent the most severely ill segment of the hospitalized population. Acquisition of infection in the ICU is associated with a grave prognosis. Awareness of patterns for nosocomial infections and the causative pathogens in different units may be of value in selecting empiric therapy.

Available data on the characteristics of infections in different types of ICU's are limited. Device-related infections involving urinary and respiratory tracts were the most common. Predominant pathogens isolated in order of frequency were *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *S. aureus* (Chandrasekar *et al.*, 1986; Thorp *et al.*, 1979).

Stratton (1990) found that when hospital-wide susceptibility patterns in the VanderBilt University Hospital were examined over several years no major changes were observed. However, when the data were analysed on a unit-by-unit basis, striking differences were found between the patterns of hospital-wide isolates and those of specific units particularly the ICU's.

1.4. ANTIBIOTIC USAGE

Organisms resistant to antimicrobial agents have more than epidemiologic significance. Resistance can affect the ease with which the afflicted patients can be treated, and this in turn may affect the outcome of the patient's illness.

McGowan (1983) reviewed the literature and reported that, "A causal relationship between antibiotic usage and resistance of hospital organisms is supported by consistent association and concurrent variation in several populations, presence of a dose - response pattern, and existence of a reasonable biologic model to explain the relationship. Virtually all reports agreed that careful, discriminating use of antimicrobial agents remains the keystone for minimizing this problem".

Davies *et al.* (1986) showed that aminoglycoside resistance in coagulase-negative staphylococci is affected by previous exposure to aminoglycosides.

The effects of long-term use of amikacin on bacterial resistance to the aminoglycosides has been evaluated quite often. All reports concur that resistance to amikacin did not increase and in some instances, e.g. *K. pneumoniae* resistance to gentamicin, netilmicin and tobramycin decreased significantly (Hesseling & Mouton, 1990; Gerding & Larson, 1985; Gerding *et al.*, 1991; Moody *et al.*, 1982; Muscato 1991).

In 1978 O'Brien *et al.* found the prevalence of bacterial resistance to antibiotics to be substantially different in two separate regions of the world, namely Paris and Boston. The comparison indicated that resistance was more prevalent in the flora of patients in Paris than Boston during the period studied. This, they suggested, was due to difference in the bacterial flora of their communities and that similar systematic comparisons of resistance prevalence in different parts of the world might help to define optimal antibiotic usage practices. Information about the prevalence of resistance is essential to the rational use of antibiotics.

In 1977, Koornhof blamed the emergence of resistant strains largely on injudicious and over-use of antibiotics by doctors in the past. In 1989, Miller concluded that the majority of today's problems of antibiotic abuse developed in an era where there were no guidelines on appropriate use or restraint on the cost of medical care. The Antibiotic Control Committee or Pharmacy and Therapeutics Committee in a hospital should play a decisive role in keeping to a minimum the number of agents needed for

optimum therapy, and in publicising guidelines for medical staff to select the least expensive yet effective agent from a drug class. The results of properly undertaken susceptibility tests by the microbiology laboratory have an important role in influencing antibiotic therapy. Various surveys have been carried out and show that there is a high proportion of antibiotic misuse (Aswapokee *et al.*, 1990; Miller, 1989; Till *et al.*, 1991).

1.5. MECHANISMS OF DRUG RESISTANCE

The emergence of antibiotic resistance is a major factor limiting long-term successful use of an antimicrobial agent. The term 'antimicrobial agent' covers all substances whether naturally occurring, synthesized or semi-synthetic but is not very precise as it includes other substances such as disinfectants. Antibiotics are substances that are obtained from micro-organisms and are able to inhibit or kill other micro-organisms. Chemotherapeutic substances have similar activity but are obtained by chemical processes rather than derived from biological sources.

The term "Antibiotic" is now often used as a trivial name to cover all these substances except disinfectants and will be used in this context in the thesis. Antibiotics differ from disinfectants in being precisely directed against specific targets in the micro-organisms. Antibiotics have a defined spectrum of activity. Some bacteria are naturally resistant to some antibiotics and naturally sensitive to others. The use of antibiotics will reduce or eliminate the numbers of sensitive bacteria creating a ecological niche which will be filled by bacteria which are naturally resistant to that antibiotic.

1.5.1. GENETICS OF RESISTANCE

Resistance to antibiotics can be divided into that which is intrinsic (i.e. a naturally occurring trait) and that which has been acquired.

Naturally occurring resistance is shared by most or all of the species and for this reason can be considered a species characteristic (e.g. resistance of *E. coli*, *K. pneumoniae* and Enterobacter species to oxacillin, clindamycin and vancomycin). Intrinsic resistance does not really pose a clinical problem since this resistance is discovered during the early phases of development of a new compound and thus clinical efficacy is never an expectation.

Acquired resistance implies that a susceptible organism has developed resistance to an agent to which it was previously susceptible. This can occur either by mutation(s) in the existing DNA of the organism, or by acquisition of new DNA. The mechanisms based on mutations include alterations of the target organelle in the microbial cell. Streptomycin for example, acts by becoming bound onto proteins derived from 30S subunit of the ribosomes. Cells that have acquired resistance produce the protein in an altered form no longer capable of binding streptomycin.

Another mechanism is exclusion of the antibiotic from the cell, for example the resistance of *E. coli* to tetracycline. Enzymes capable of destroying or modifying the antibiotic might be elaborated, such as β-lactamases capable of opening the β-lactam ring of cephalosporins and penicillins. Finally, the blocked reaction could be bypassed by a

different pathway: resistance to trimethoprim can be brought about by modifying the metabolic pathway which is interrupted by trimethoprim.

Acquisition is the transfer of DNA from one bacterium to another, and occurs by one of several processes (Datta, 1984; Murray & Hodel-Christian, 1991; van den Ende, 1989; Williams, 1984):

- Conjugation: It is generally accepted that this is the most common mechanism of transfer of resistance genes. Cell-to-cell contact is made and DNA from one cell,the donor, is transferred to another cell, the recipient. The ability to conjugate is normally encoded by conjugative plasmids or less commonly by conjugative transposons. Such gene transfer occurs readily among Gram-negative bacilli and may occur not only between identical species but also across species and genera.

- Transduction: This is the transfer of genes by bacteriophage particles. Extrachromosomal genes are transmitted by means of bacteriophages and can only occur between donor and recipient bacteria that share appropriate cell surface receptors for the transducing phage. Transduction is particularly important for plasmid transfer between Gram-positive cocci among which conjugation is less common.

- Transformation: Free or naked DNA may be taken up, internalised and integrated into the DNA of a living bacterium.

- Plasmids are extrachromosomal elements of DNA that are not essential for the survival of bacterial cell. They vary in size from <1 to >300x10^6 daltons. They can replicate autonomously (independently of the chromosome).

Plasmids can contain very different numbers and types of genes (Datta, 1984; Murray & Hodel-Christian, 1991; van den Ende, 1989; Williams, 1984), and can thus encode a number of different traits. A few examples of the traits that can be carried are: antibiotic resistance (known as resistance or R plasmids); carbohydrate fermentation; toxin production; bacteriocin production. Plasmids also differ in other characteristics, such as the ability of some plasmids to mediate their own transfer by conjugation - conjugative plasmids. Plasmids that cannot mediate their own transfer are termed nonconjugative plasmids. One may see co-transfer of nonconjugative plasmids. This is described as mobilization and depends on the presence in the nonconjugative plasmid of "mobilization" or mob genes.

Transposons are specific sequences of DNA that have the ability to move from one DNA molecule to another independent of the cell's homologous recombination system. Also termed 'Jumping genes', they are able to detach themselves from chromosomes, plasmids and bacteriophages and re-insert themselves into DNA elsewhere. Thus genes coding for resistance to a particular antibiotic may be added to a plasmid which already codes for resistance to one or more agents. Unlike plasmids they are not able to replicate independently. They must therefore be maintained as part of a functional self-replicating DNA molecule such as a plasmid or bacteriophage. The ability of DNA to move from organism to organism has had a major effect on increasing resistance. The

major impact of transposons on the emergence of antibiotic resistance is that they can expand the host range to which resistance genes can be spread. Plasmids in general have a narrower range of organism in which they are stable, whereas transposons are less restricted e.g. the ability of gram-positive transposons to transpose in gram-negative organisms.

Plasmid and transposon-mediated resistance are the most common and important forms of acquired resistance and have been aptly referred to as "infectious" antibiotic resistance.

Antibiotic resistance is increasing amongst almost all bacterial species. The epidemiological factors in this increase are complex (Williams, 1984) and are considered below:

- acquisition of resistance by which bacteria receive their resistance genes is either chromosomal: mutation, tranduction and transformation or extrachromosomal (plasmids): transduction and transfer.

- mechanisms of resistance that may be present are the alteration of the target organ in the microbial cell, the exclusion of the antibiotic from the cell, elaboration of enzymes capable of destroying or modifying the antibiotic and the by-pass of the blocked reaction by a different pathway.

- means of dissemination of resistant organisms are case to case transfer, acquisition from carriers and from the inanimate environment including food. Virulence and transmissibility of the organism, use of antibiotics and opportunities for infection in a hospital are all factors influencing the spread of resistant organisms.

Two types of clinical problems may arise from antibiotic-resistant bacteria, namely epidemic and endemic disease. Endemic diseases may cause large numbers of single episodes of infection creating treatment problems for individual patients. The acquisition of antibiotic resistance in the normal flora of man provides a gene pool of resistance which can either transfer to more virulent species or give rise to infection themselves in immunologically deficient patients (Williams, 1984).

1.6. RESEARCH OBJECTIVES

This project was undertaken to:

- monitor antibiotic resistance patterns in a Port Elizabeth hospital.

- follow pattern changes over a three year period at different sampling points within the hospital.

- report, assess and compare the resistance data from the Provincial Hospital, Port Elizabeth, with other studies reported from South Africa and abroad.

- establish a computer program whereby the data could be easily collated into meaningful information.

- determine whether this information was of value to the medical staff and to offer a continuing service of this nature to the hospital and in doing so, assist in the control of antibiotic resistance and the cost effective use of these drugs.

- correlate resistance patterns with antibiotic usage in the hospital.

CHAPTER 2

2. MATERIALS & METHODS

In the 3 year study period 1989, 1990 and 1991, all specimens for microbiological examination from PHPE which were processed by the South African Institute for Medical Research pathology laboratories were included in this study. Over this period, 5580 patient records containing 9888 isolates with susceptibility results were entered into the computer program.

Duplicate cultures from patients were excluded from this study unless the susceptibility pattern was significantly different i.e. sensitive changed to (became) resistance. This sorting was performed manually by the investigator. Special attention was paid to the Intensive Care Units (ICU) patients reports being kept together for as long as they were in the unit and each report was scrutinized for repeated organisms with identical susceptibility patterns.

The organisms were identified using standard laboratory techniques including: API 10S, API 20E, API 20NE (API Systems, BioMerieux) for the Gram-negative bacilli, catalase, DNase, Staphaurex (Murex), aesculin hydrolysis, bile tolerance, pyruvate and 6,5% NaCl for the Gram-positive cocci. In certain instances full identification was not carried out because either, it would mean a delay of a further day in the report reaching the ward, or it was deemed to be cost efficient for the hospital.

2.1 ANTIMICROBIAL SUSCEPTIBILITY TEST METHOD

Numerous methods are available for testing the sensitivity of bacteria to antimicrobial agents. These include :-

Disc diffusion method.

Agar diffusion / dilution method.

Break-point determination.

Minimum inhibitory concentration. (MIC)

The disc diffusion method is the one commonly used in routine diagnostic laboratories where there is a need to combine accuracy with speed.

There are different ways of performing disc diffusion tests, the most accepted being:

- the International Collobrative study (ICS)
- the Kirby-Bauer (KB)
- the comparative method of Stokes.

The ICS and KB methods rely for interpretation on comparing measured zones with a scale prepared from regression lines relating zone size to minimum inhibitory concentration (MIC). The comparative (Stokes) method depends on comparison between zones seen with the test organism and those of a known sensitive control. The test and control organisms are inoculated onto one plate. This method was employed for the purpose of this study (Stokes & Ridgeway, 1987).

2.2. MEDIA USED IN THIS STUDY:

Diagnostic Sensitivity Test (DST) Agar (MAST)

Formula:	Beef Extract	7.0 g
	Uridine	0.05 g
	Peptone	13.5 g
	NaCl	5.0 g
	Agar	12.0 g
	pH	7.3

Method per litre:

1. Suspend by swirling 37.5 g in 1 litre distilled water.
2. Steam for 1 hour to dissolve.
3. Autoclave at 120°C (15 p.s.i.) for 15 minutes.
4. Cool at 50°C.
5. Pour plates 4 mm deep.

Saline (0.85%)

Formula:	NaCl	85 g
	Distilled water	10 litres.

Method:

Dissolve and dispense 6 ml into tubes.

Cap and autoclave at 121°C (15 p.s.i.) for 15 minutes.

MacFarland 0,5 Standard (108 organisms/ml)

Solution 1 (0.048) M BaCl)

BaCl2 - 2H20	1,17 g
Distilled Water	100 ml

Solution 2 (0,35 N H2S04)

a)	H2SO4	0,35 ml
	Distilled Water	99,65 ml

b) Add 1 ml of (a) to 100 ml Distilled Water.

Final Solution (100 ml)

Add 0.5 ml solution 1 (0,048 M BaCl2)

to

99,5 ml Solution 2 (0,35 N HsSO4)

Dispense amounts into sealed containers as required by the laboratory.

2.3. TEST ORGANISMS

The test organisms used in this study were isolated in the SAIMR routine diagnostic laboratory from a variety of specimens. The primary isolation plates were inoculated directly from the specimens, each type of specimen requiring a different selection of plates. This was to ensure that all possible pathogens would be isolated if present. These plates were incubated under optimal conditions and inspected for growth the following day.

All clinically significant organisms were set aside for sensitivity and identification tests. Where a sensitivity result after 24 hours was useful in the case of urine specimens and only one organism was usually present in significant numbers a sensitivity test was performed directly from the urine. If the bacterial count was >100,000 organisms per ml this was considered significant growth.

If after incubation the inoculum was too heavy or too light, the test was repeated from the primary plates.

2.4. METHOD OF INOCULATION

It is not desirable to test a single colony as there may be variation in sensitivity (Stokes & Ridgeway, 1987). Therefore 3 to 5 discrete colonies were selected, touched and emulsified in saline. Inoculum density was compared with the 0.5 MacFarland standard and adjusted if necessary. Once the turbidity was correct the suspension was ready for inoculation onto the sensitivity test agar.

2.5. CONTROL ORGANISMS

The following were the control organisms used until 30th June 1990:

For organisms isolated from urine:
Escherichia coli NCTC 10418

For organisms isolated from all other sites:
Staphylococcus aureus NCTC 6571

For Pseudomonas species:
Pseudomonas aeruginosa NCTC 10662

The control must be an organism known to respond to treatment with normal doses of the antimicrobial agent and the choice depends on the site of infection and the concentration of the drug attainable there. Agents which are excreted by the kidneys produce high concentrations in the urine and more resistant organisms are likely to respond to treatment. Therefore, a more resistant control should be used. If interpretation is based on the use of controls as originally defined, coliform organisms causing systemic infections treatable with normal doses of some agents may be misinterpreted as having intermediate susceptibility. This is one of the reasons why many laboratories have modified the method so that Gram-negative bacilli are compared with *E. coli* control and Gram-positive cocci with staphylococcus control.

After consultation with leading microbiologists in the country the control organisms used were changed. The following are the control organisms used as from 1st July 1990:

For coliform organisms:
Escherichia coli NCTC 10418

For Gram-positive organisms:
Staphylococcus aureus NCTC 6571

For Pseudomonas species:
Pseudomonas aeruginosa NCTC 10662

The DST agar plate was inoculated with the aid of a rotary plater, an instrument with a turntable as shown in Figure 2.1. A swab was moistened with the control organism and the DST agar plate inoculated from the outside towards the centre up to the dividing ring while the plate rotated on the turntable. This was repeated using the test organism but inoculating from the centre outwards to the ring.

Figure 2.1. The "MAST" rotary plater.

2.6. DISCS CONTAINING ANTIMICROBIAL AGENTS

One ring containing six discs was used per plate. Single discs were used when necessary. Disc concentrations of antimicrobial agents were as listed below.

Penicillin	2 Units
Ampicillin	10 ug (25 ug urine specimens)
Oxacillin	1 ug
Piperacillin	100 ug
Cefamandole	30 ug
Tetracycline	10 ug
Cotrimoxazole	25 ug
Erythromycin	10 ug
Clindamycin	2 ug
Fusidic acid	10 ug
Kanamycin	30 ug
Chlorampenicol	25 ug
Gentamicin	10 ug
Tobramycin	10 ug
Neticmicin	10 ug
Amikacin	10 ug
Cefoxitin	30 ug
Cefotaxime	30 ug
Ceftazidime	30 ug
Imipenem	10 ug
Ofloxacin	5 ug
Sulfisoxazole	100 ug
Nalidixic Acid	30 ug
Nitrofurantoin	50 ug
Nicene	60 ug
Vancomycin	30 ug
Norfloxacin	10 ug
Methicillin	5 ug incubation at 30°C
Ciprofloxacin	5 ug

2.7. SELECTION OF ANTIMICROBIALS FOR ROUTINE TESTING

The agents are chosen according to:

- Availability from hospital pharmacy.
- Appropriateness for therapeutic use.

The appropriate ring containing the discs required was carefully placed onto the inoculated plate. The discs were on the edge of the circle where the control and test organisms were adjacent to one another.

As soon as possible and not later than 15 minutes after inoculation of plates, the antibiotic discs were applied so that diffusion and growth proceeded simultaneously.

Once the discs were placed on the agar surface, they were not removed, since initial contact of the disc to the agar surface would immediately result in the diffusion process. These plates were incubated within 15 minutes at 35°C overnight.

Figure 2.2. DST agar plate showing control organism on the outside, test organism on the inside. A = resistant B = sensitive.

2.8. INTERPRETATION OF RESULTS

Zones of inhibition of the test organism were compared with those of the control. A millimetre rule was used for accuracy. Provided the inoculum was optimal, the results were reported as follows:- Sensitive: Zone radius equal, or wider than the control. Intermediate: Zone radius smaller than the control by up to 3mm. Resistant: Zone radius more than 3mm smaller than control (Figure 2.2.). This interpretation is not valid for some tests with penicillinase producing Staphylococci (Stokes & Ridgeway, 1987).

2.9. METHICILLIN SUSCEPTIBILITY TESTING

As methicillin resistant staphylococci often appear fully sensitive when tested in the normal way, a separate DST agar plate was used and incubated at 30°C. The control organism was spread with a swab over half of the agar place. The other half was divided into two and the quarters were inoculated with a test organism each.

2.10. COMPUTER PROGRAM

After sorting, the reports were ready for processing. Manual computation of such data is tedious and subject to error, and analysis is ideally performed by a computer (Chan *et al.*, 1988).

A computer program "Antibug" was written by Professor CEJ Botha (Rhodes University) to provide a broad data base including: Date, laboratory number, Ward, Specimen type, sex, organism name and susceptibility result. The program was written in dBASE III but ran independently off dBASE II and could be used in laboratories which were not computerised and have an IBM compatible PC with a hard drive. The program was later modified to provide easily interpretable printed reports containing various results specified by the user.

2.11. STATISTICAL METHODS

Using the null hypothesis, a test for proportions using a statistic was applied. There is a 5% level of significance where the value is greater than 1,96. There is a 1% level of significance where the value is greater than 2,33.

2.12. DRUG USAGE IN THE HOSPITAL

Information regarding the usage of antimicrobial agents was obtained from the hospital pharmacy for the three year period.

CHAPTER 3

3. RESULTS

Antibiotic resistance was determined for a range of bacterial species from clinical specimens submitted to the S.A.I.M.R. Pathology Laboratory from PHPE. Over the three year period 1989-1991, 5580 patient records produced 9888 isolates with sensitivity results. Table 3.1. summarises the total numbers of in-patients, patient records and isolates for this period.

Table 3.1. The total numbers of in-patients, total patient records and total isolates with susceptibility results PHPE.

Year	Number of in-patients	Number of patient records	Number of isolates
1989	160467	1303	3455
1990	144342	2156	3215
1991	142170	2121	3218

The data was logged onto "Antibug" the computer program developed for recording and reporting the 40 sampling centres (wards), 95 organisms, 33 antibiotics and 36 types of clinical specimens.

Thus early in the investigation decisions had to be made with regard to the inclusion or exclusion of the various figures and in what format the data would be reported.

Decisions that needed to be made were:

- Whether all individual sampling centres were to be reported in the results. An early analysis of the results showed that the only significant differences occurred between the combined wards of the whole hospital on the one hand and the ICU on the other. This has been collaborated by other workers (Stratton, 1990; Liebowitz & Koornhof, 1990).

- It was decided in 1990 that the Out-patients department (OPD) should be evaluated as a separate entity in order to demonstrate a possible nosocomial component. Therefore OPD records were logged accordingly for 1990 and 1991.

  However, the numbers of isolates recorded from OPD except in the case of urine specimens, were very low. Therefore the comparison between organisms showing significant patterns of increasing resistance from the whole hospital and ICU, and OPD was not considered feasible.

- Given a dissimilar range of antibiotics used for urinary infections in comparison to other infections, it was decided to consider urine specimens separately from all other specimens.

In the case of the number of isolates from urine specimens the numbers were sufficiently high to make a comparison for OPD and the whole hospital to demonstrate a possible nosocomial component.

Antibiotic resistance patterns are considered below for the aforementioned organisms isolated. They were selected according to the frequency of isolation in the hospital, and the fact that they are cited as the most common nosocomial pathogens in the literature (Crowley *et al.*, 1986; Smith *et al.*, 1989).

3.1. GRAM POSITIVE COCCI

The 1989 figures for staphylococci presented below include the methicillin resistant strains. It was decided in 1990 that it would be interesting to review the methicillin sensitive and resistant isolates separately and compare the results. Therefore the figures for 1990 and 1991 reflect methicillin resistant and methicillin sensitive isolates separately.

3.1.1. *STAPHYLOCOCCUS AUREUS*

The annual resistance patterns of *S. aureus* from PHPE to a range of antibiotics is presented for the period, 1989 to 1991 for the whole hospital (Figure 3.1.) and the ICU (Figure 3.2.). Figures 3.3. and 3.4. report the mean of percentage resistance for isolates of methicillin sensitive *S. aureus* and Table 3.2. presents a comparison of percentage resistance between the whole hospital and the ICU over 1990 and 1991.

The annual resistance patterns for methicillin resistant *S. aureus* are presented for the whole hospital (Figure 3.5.) and the ICU (Figure 3.6.) over the period 1990 and 1991. In 1990 and 1991, 67 and 88 isolates were recorded for the whole hospital and 15 and 27 for the ICU respectively. Figures 3.7. and 3.8. report the mean of percentage resistance for isolates of methicillin resistant *S. aureus* and Table 3.3. presents a comparison of percentage resistance between the whole hospital and the ICU over the two year period.

A statistical evaluation of the changing patterns of resistance of staphylococcal isolates (MSSA, MSSE, MRSA, MRSE) for the whole hospital and the ICU is reported in Tables 3.4. and 3.5., respectively.

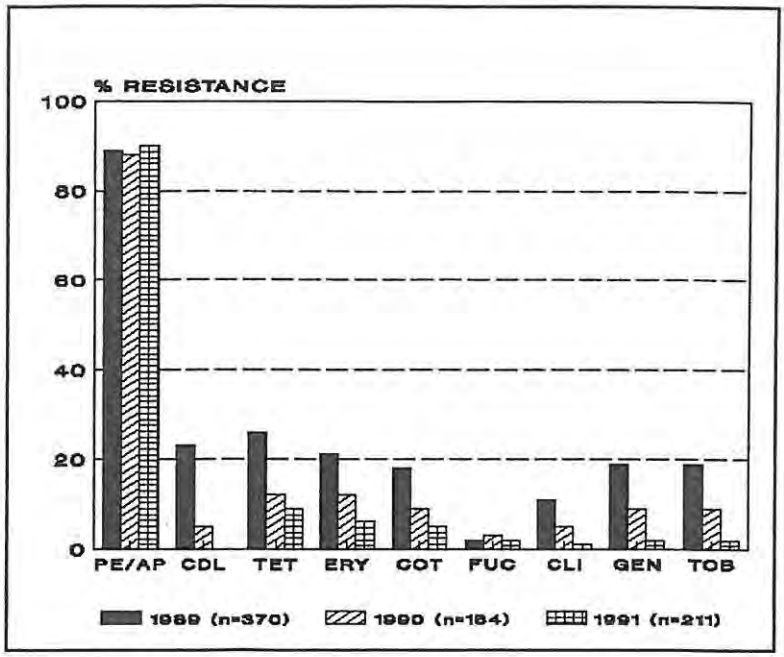

Figure 3.1. Percentage of isolates of MSSA from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

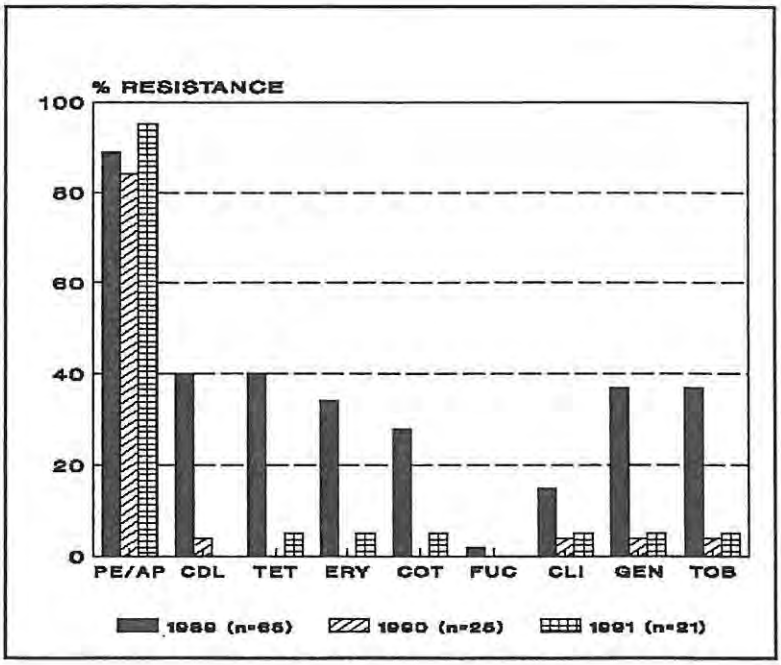

Figure 3.2. Percentage of isolates of MSSA from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

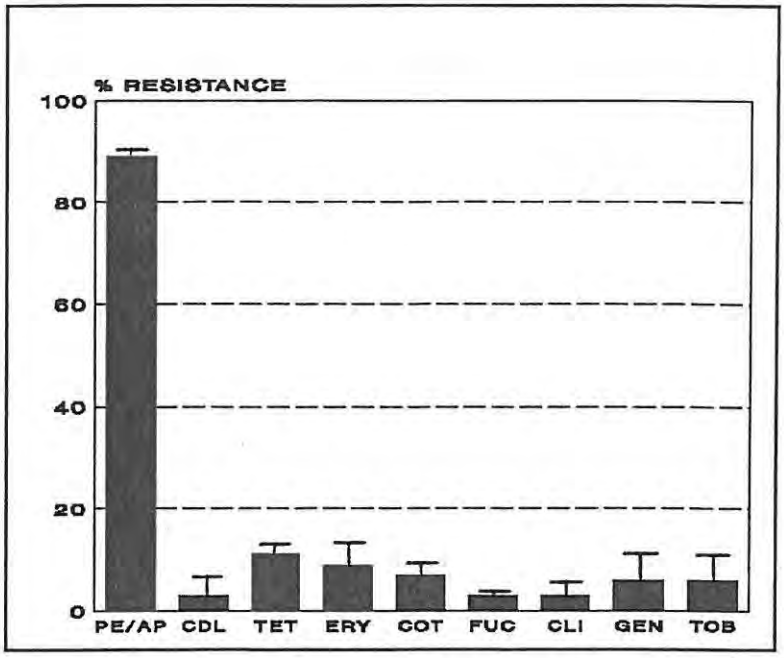

Figure 3.3. The mean of resistant isolates of MSSA for PHPE (whole hospital). Results reported with one standard deviation.

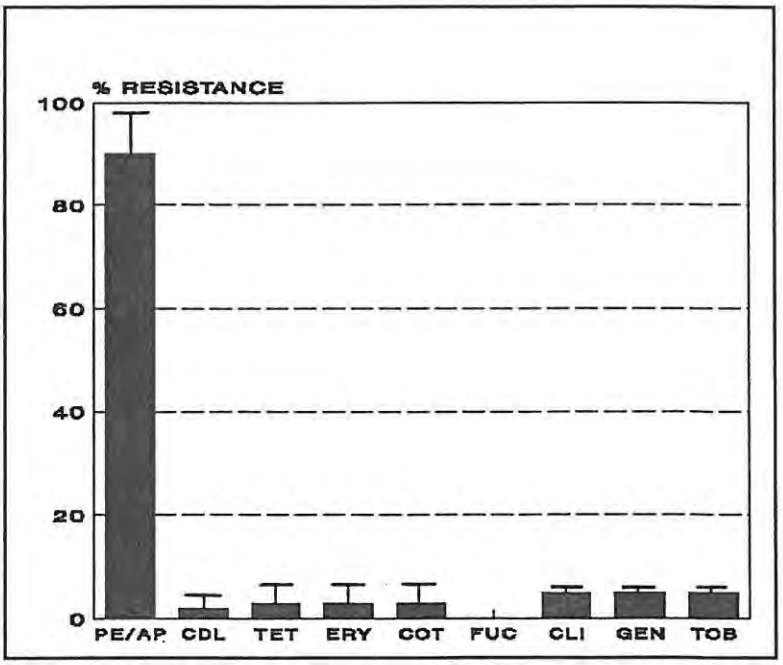

Figure 3.4. The mean of resistant isolates of MSSA for PHPE (ICU). Results reported with one standard deviation.

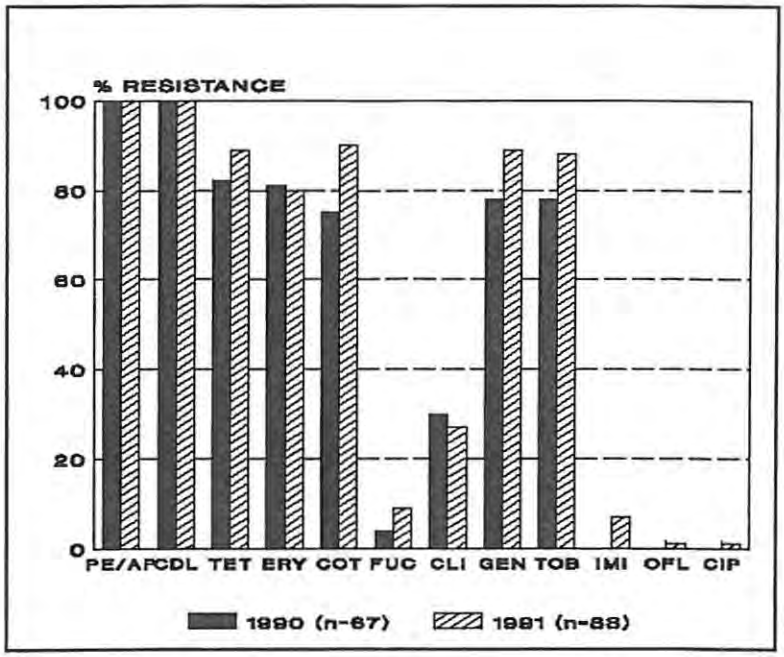

Figure 3.5. Percentage of isolates of MRSA from PHPE (whole hospital) showing resistance to a range of antibiotics over the two year period 1990-1991.

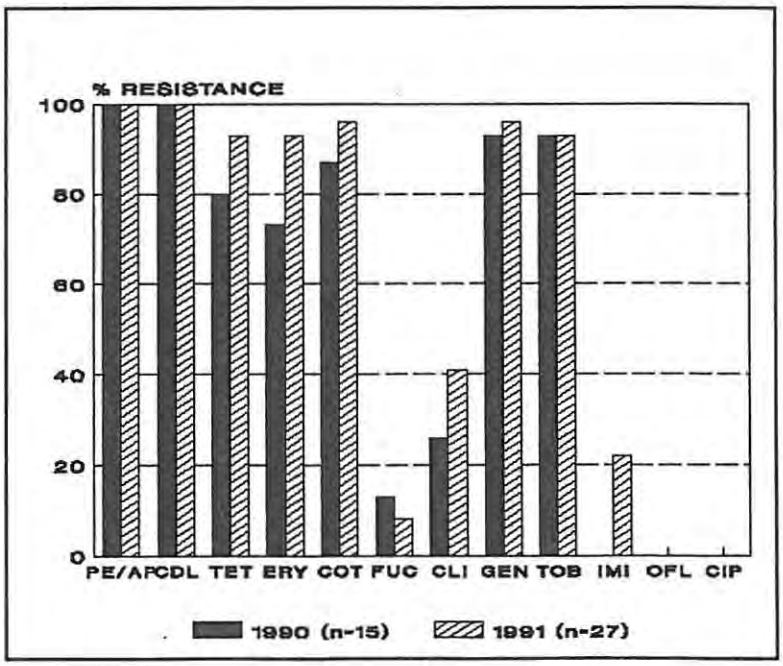

Figure 3.6. Percentage of isolates of MRSA from PHPE (ICU) showing resistance to a range of antibiotics over the two year period 1990-1991.

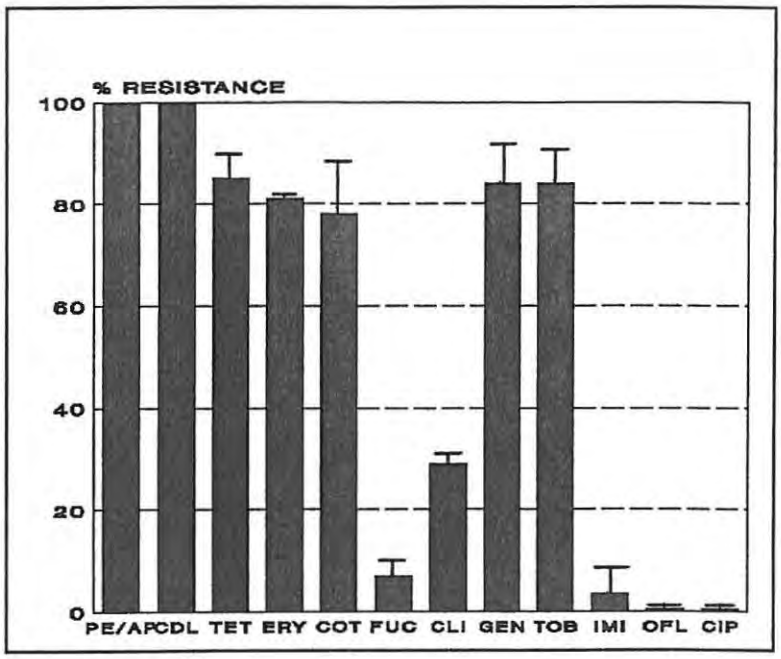

Figure 3.7. The mean of resistant isolates of MRSA for PHPE (whole hospital). Results reported with one standard deviation.

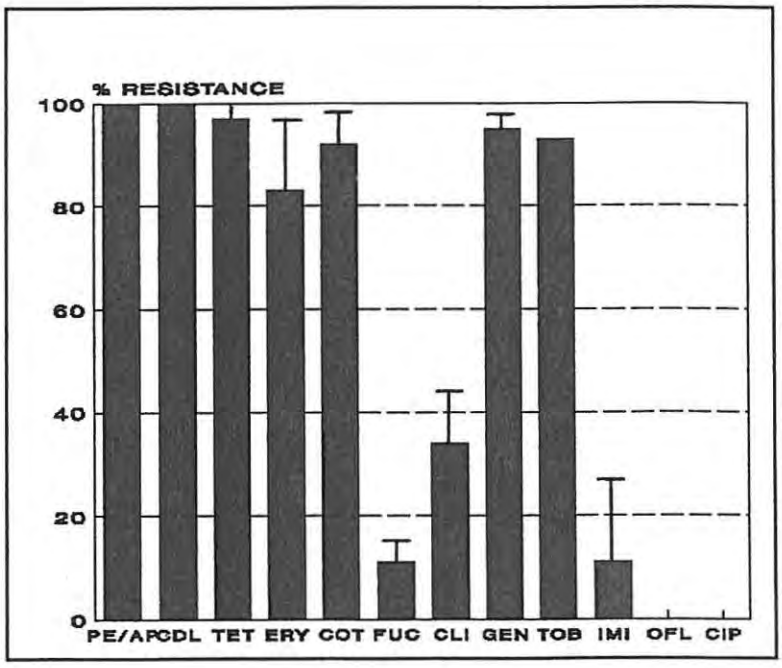

Figure 3.8. The mean of resistant isolates of MRSA for PHPE (ICU). Results reported with one standard deviation.

In 1989 the MRSA isolates were included in the analysis, resulting in the peaks in each instance, except for fucidin. The resistant isolates occurred in a lower percentage in the ICU than the whole hospital except for clindamycin, gentamicin and tobramycin (Table 3.2.). Over 80% of the isolates showed resistance to penicillin/ampicillin while in all other instances the percentage resistance was below 13%.

The decrease in the percentage resistance of methicillin sensitive *S. aureus* isolates from the whole hospital, to cefamandole, erythromycin, clindamycin and the aminoglycosides tested, was statistically significant (Table 3.4.).

In 1989, 1990 and 1991 the percentage of methicillin resistant strains was 22%; 29% and 29% respectively (Table 3.9.). In both the whole hospital and the ICU the number of methicillin resistant *S. aureus* isolates was found to increase over each year.

MRSA isolates showed a higher percentage resistance in the ICU generally, particularly to cotrimoxazole and aminoglycosides in 1990 and to erythromycin, clindamycin and imipenem in 1991 (Table 3.3. and Figures 3.5. and 3.6.).

The incidence of resistance was below 10% of the whole hospital isolates only in the case of fucidin, imipenem and the quinolones, and of the ICU isolates only in the case of fucidin and the quinolones. The trend of increasing resistance in the whole hospital to cotrimoxazole and imipenem was found to be statistically significant and in the case of the ICU only imipenem proved to a statistically significant increase.

Table 3.2. Comparison of percentage resistant isolates of *S. aureus* (MSSA) between the whole hospital and the ICU over the period 1990 and 1991.

	1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**
PE/AP	88	84	90	95
CDL	5	4	0	0
TET	12	0	9	5
ERY	12	0	6	5
COT	9	0	5	5
FUC	3	0	2	0
CLI	5	4	1	5
GEN	9	4	2	5
TOB	9	4	2	5
IMI	NT	0	NT	0
OFL	NT	0	NT	0
CIP	NT	0	NT	0
PIP	0	0	0	0
VAN	0	0	0	0

NT = not tested.

Table 3.3. Comparison of percentage resistant isolates of methicillin resistant *S. aureus* (MRSA) between the whole hospital and the ICU over the period 1990 and 1991.

	1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**
PE/AP	100	100	100	100
CDL	100	100	100	100
TET	82	80	89	93
ERY	81	73	80	93
COT	75	87	90	96
FUC	4	13	9	8
CLI	30	26	27	41
GEN	78	93	89	96
TOB	78	93	88	93
IMI	0	0	7	22
OFL	0	0	1	0
CIP	0	0	1	0
PIP	0	0	0	0
VAN	0	0	0	0

Table 3.4. Test for proportions comparing percentage resistance of staphylococcal isolates in PHPE (whole hospital) over the period 1990/1991.

Antibiotic	MSSA		MSSE		MRSA		MRSE	
PE/AP	0,6113	#	1,0585	#	0	#	0	#
CDL	2,9380	**	2,6784	**	0	#	0	#
TET	0,9338	#	1,1425	#	1,2157	#	3,8043	**
ERY	1,9877	*	1,1498	#	0,1559	#	0,1822	#
COT	1,4861	#	0,8120	#	2,4266	**	0	#
FUC	0,6082	#	0,2293	#	1,2894	#	1,8623	#
CLI	2,1804	*	1,1107	#	0,4092	#	0,1565	#
GEN	2,8763	**	0,3773	#	1,8149	#	0,5672	#
TOB	2,8763	**	0,7104	#	1,6306	#	1,4510	#
IMI	0	#	0	#	2,5736	**	0,6938	#
OFL	0	#	0	#	0,9428	#	0,6344	#
CIP	0	#	0	#	0,9428	#	1,5972	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.5. Test for proportions comparing percentage resistance of staphylococcal isolates in PHPE (ICU) over the period 1990/1991.

Antibiotic	MSSA		MSSE		MRSA		MRSE	
PE/AP	1,2587	#	1,4114	#	0	#	0	#
CDL	1,0206	#	1,0719	#	0	#	0	#
TET	1,0513	#	0,4913	#	1,1368	#	3,1786	**
ERY	1,0513	#	0,1782	#	1,6038	#	0,1350	#
COT	1,0513	#	0,5367	#	0,9507	#	0	#
FUC	0	#	0,6207	#	0,4935	#	0,5066	#
CLI	0,1623	#	1,1450	#	1,0163	#	0,9854	#
GEN	0,1623	#	0,5129	#	0,2561	#	1,0495	#
TOB	0,1623	#	0,8386	#	0	#	0	#
IMI	0	#	0	#	2,7596	**	2,0071	*
OFL	0	#	0	#	0	#	1,5000	#
CIP	0	#	0	#	0	#	1,5000	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

3.1.2. *STAPHYLOCOCCUS EPIDERMIDIS*

The percentage of resistant isolates of *S. epidermidis* from PHPE to a range of antibiotics is presented for the period 1989 to 1991. Figures 3.9. and 3.10. present results of annual resistance patterns and the mean of percentage resistance of methicillin sensitive *S. epidermidis* is reported in Figures 3.11. and 3.12. for the whole hospital and the ICU respectively. Table 3.6. presents a comparison of percentage resistance between the whole hospital and ICU over 1990 and 1991.

The results of annual resistance patterns of methicillin resistant *S. epidermidis* are presented for the whole hospital (Figure 3.13.) and the ICU (Figure 3.14.) over the period 1990 and 1991. In 1990 and 1991, 108 and 125 isolates were recorded for the whole hosital and 56 and 54 for the ICU, respectively. Figures 3.15. and 3.16. report the mean of percentage resistance for isolates of methicillin resistant *S. epidermidis* and Table 3.7. presents a comparison of percentage resistance between the whole hospital and the ICU over the two year period.

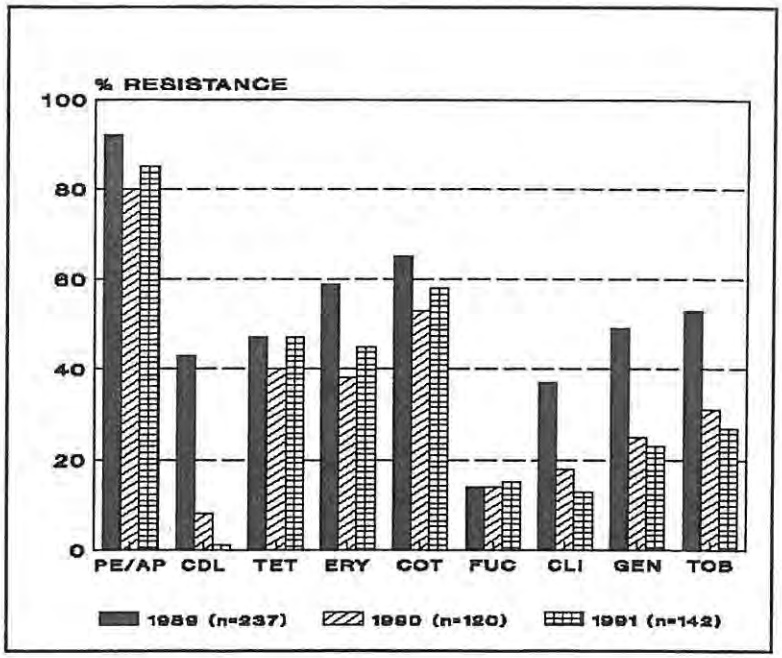

Figure 3.9. Percentage of isolates of MSSE from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

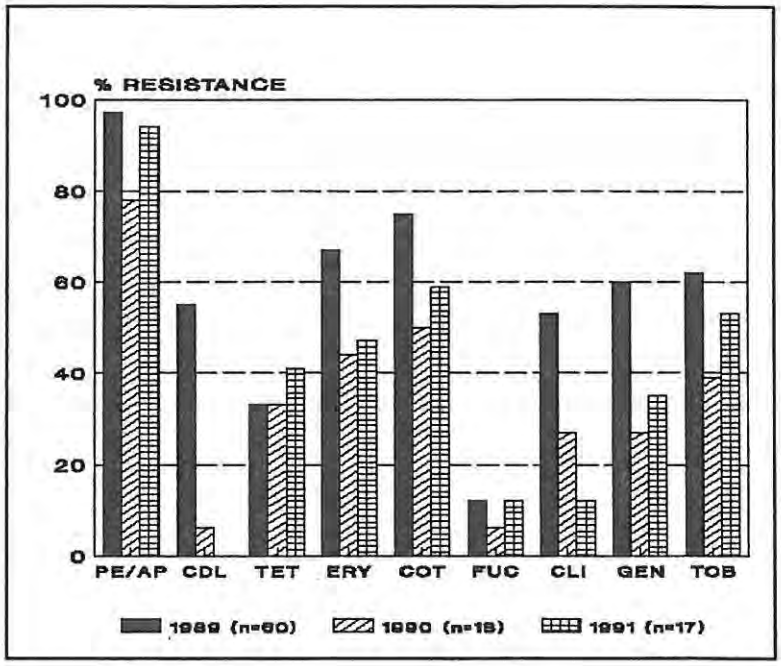

Figure 3.10. Percentage of isolates of MSSE from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

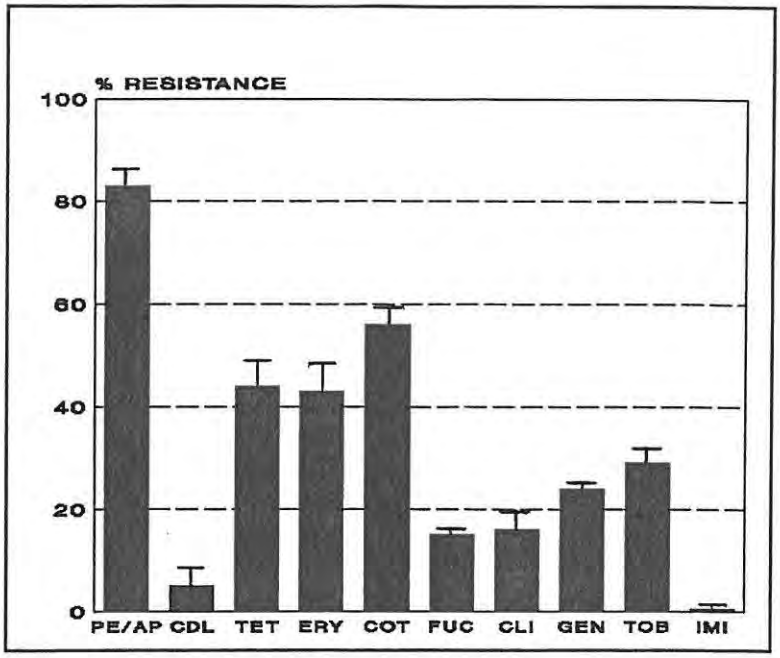

Figure 3.11. The mean of resistant isolates of MSSE for PHPE (whole hospital). Results reported with one standard deviation.

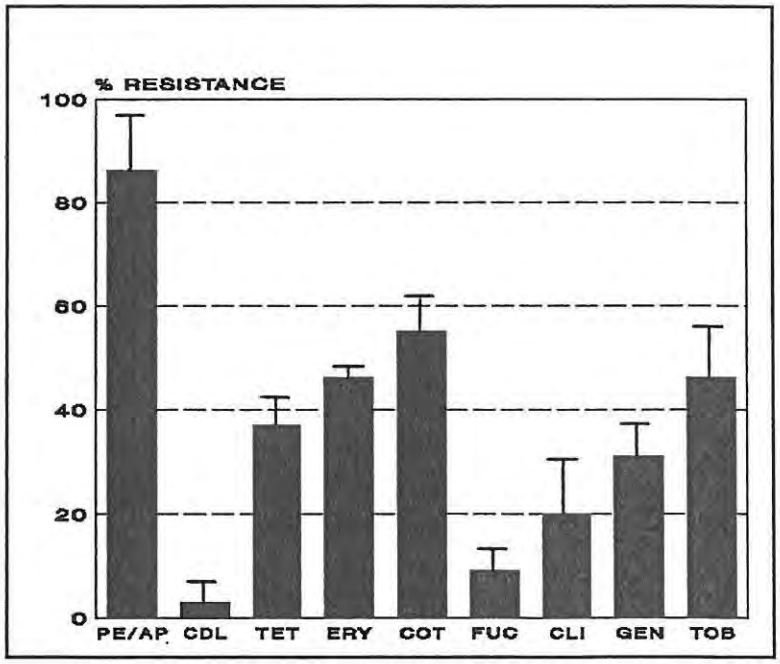

Figure 3.12. The mean of resistant isolates of MSSE for PHPE (ICU). Results reported with one standard deviation.

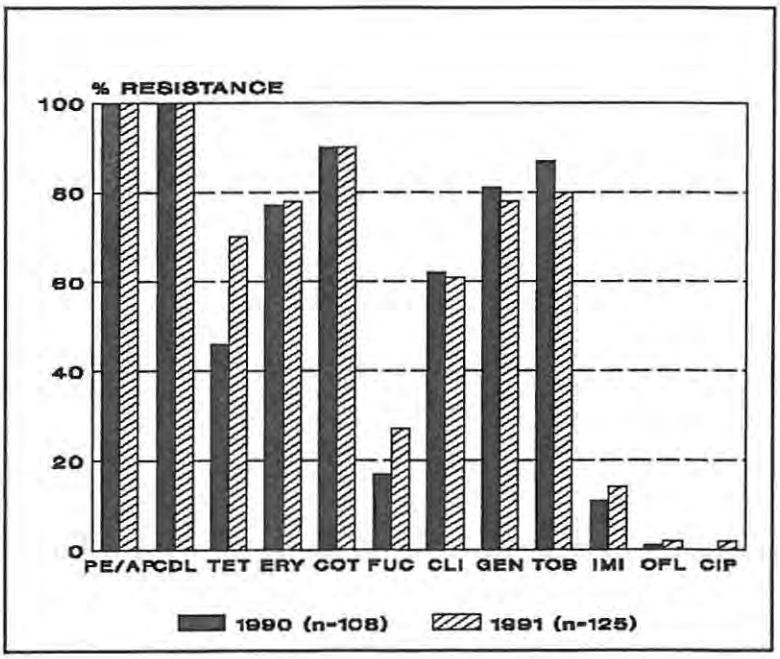

Figure 3.13. Percentage of isolates of MRSE from PHPE (whole hospital) showing resistance to a range of antibiotics over the two year period 1990-1991.

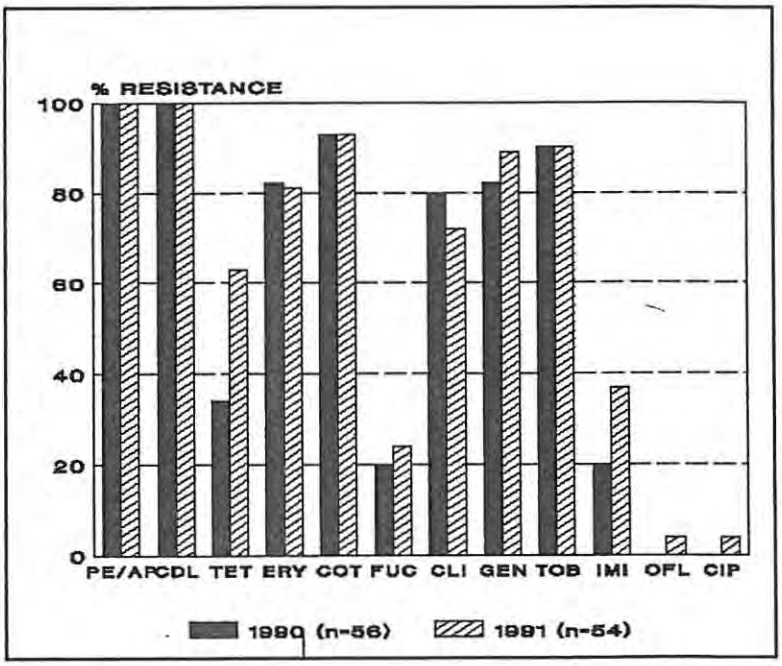

Figure 3.14. Percentage of isolates of MRSE from PHPE (ICU) showing resistance to a range of antibiotics over the two year period 1990-1991.

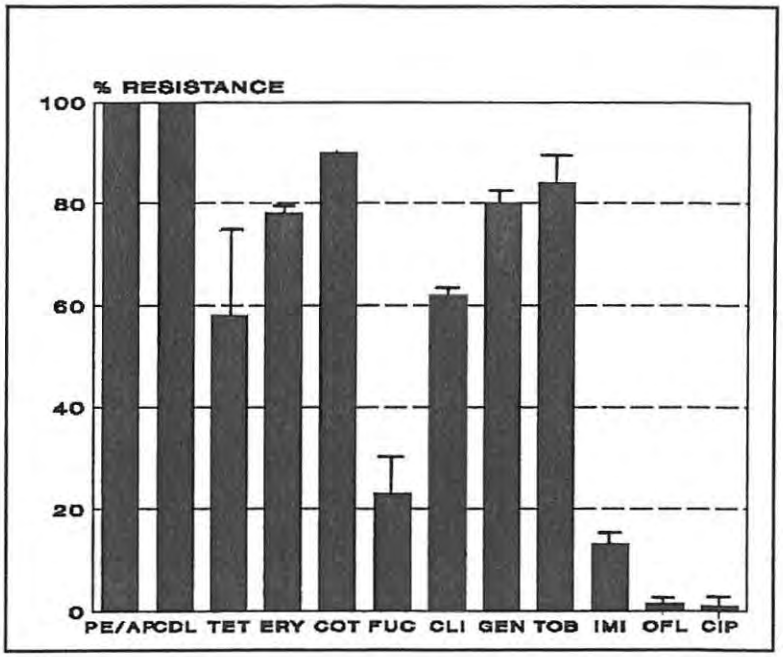

Figure 3.15. The mean of resistant isolates of MRSE for PHPE (whole hospital). Results reported with one standard deviation.

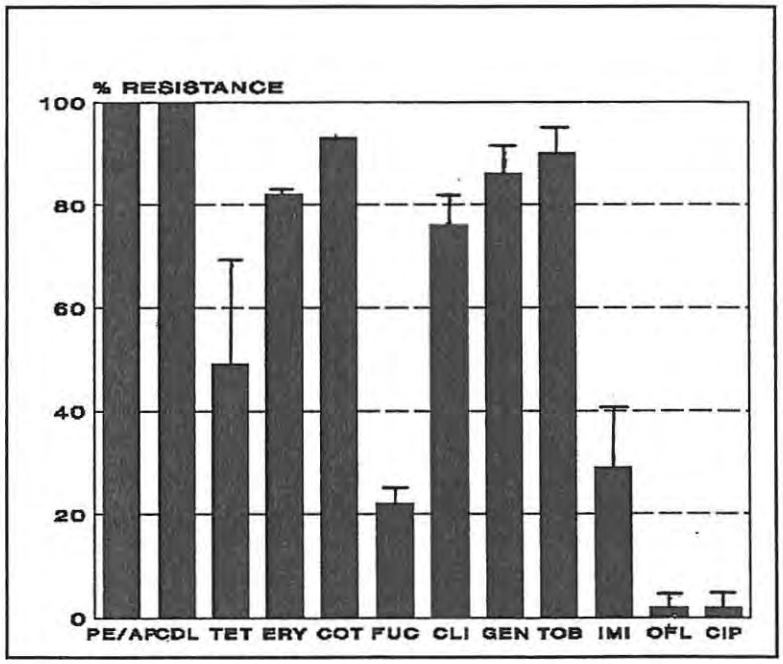

Figure 3.16. The mean of resistant isolates of MRSE for PHPE (ICU). Results reported with one standard deviation.

The peaks in 1989 (Figures 3.9. and 3.10.) reflect the inclusion of the methicillin resistant isolates. In the ICU penicillin/ampicillin, erythromycin, clindamycin and the aminoglycosides showed a higher percentage resistance than the whole hospital (Figures 3.11. and 3.12.). The decrease in percent resistance to cefamandole in the whole hospital was statistically significant (Table 3.4.).

Table 3.8. presents the mean of percentage resistance of staphylococcal isolates (MSSA, MSSE, MRSA, MRSE) for the whole hospital.

In 1989, 1990 and 1991, the percentage of methicillin resistant strains was 43%, 47% and 47% respectively (Table 3.9.). In the whole hospital the number of isolates of methicillin resistant *S. epidermidis* was found to increase and that from the ICU to marginally decrease.

Only in the cases of fucidin, imipenem and the quinolones was the resistance below 40 percent. Over 60% of isolates showed resistance to erythromycin, cotrimoxazole, clindamycin and the aminoglycosides.

The change in percentage resistance to tetracycline proved to be statistically significant in isolates from both the whole hospital and the ICU and to imipenem in the ICU only (Figures 3.13. and 3.14. and Tables 3.4. and 3.4.).

The mean of percentage resistance over 1990 and 1991 of staphylococcal isolates shows that *S. epidermidis* is more resistant than *S. aureus* except to penicillin/ampicillin in the methicillin sensitive isolates and tetracycline, erythromycin and gentamicin in the methicillin resistant isolates (Table 3.8.).

Table 3.10. presents a comparison of the percentage resistance and intermediate susceptibility to the newer agents tested for against staphylococci. The intermediate strains increased from 1990 to 1991 except for *S. aureus* and in 1991, the percentage of isolates showing intermediate susceptibility is higher than the resistance figure to each agent against MRSA, MRSE and *S. epidermidis*.

Table 3.6. Comparison of percentage resistant isolates of *S. epidermidis* (MSSE) between the whole hospital and the ICU over the period 1990 and 1991.

	1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**
PE/AP	80	78	85	94
CDL	8	6	1	0
TET	40	33	47	41
ERY	38	44	45	47
COT	53	50	58	59
FUC	14	6	15	12
CLI	18	27	13	12
GEN	25	27	23	35
TOB	31	39	27	53
IMI	1	0	0	0
OFL	0	0	0	0
CIP	0		0	0
PIP	0	0	0	0
VAN	0	0	0	0

Table 3.7. Comparison of percentage resistant isolates of methicillin resistant *S. epidermidis* (MRSE) between the whole hospital and the ICU over the period 1990 and 1991.

	1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**
PE/AP	100	100	100	100
CDL	100	100	100	100
TET	46	34	70	63
ERY	77	82	78	81
COT	90	93	90	93
FUC	17	20	27	24
CLI	62	80	61	72
GEN	81	82	78	89
TOB	87	90	80	90
IMI	11	20	14	37
OFL	1	0	2	4
CIP	0	0	2	4
PIP	0	0	0	0
VAN	0	0	0	0

Table 3.8. Average percentage resistance of staphylococci 1990/1991.

Antibiotic	**MRSA**	**MRSE**	**MSSA**	**MSSE**
PE/AP	100	100	90	83
CDL	100	100	3	4
TET	86	58	11	44
ERY	81	78	9	42
COT	83	90	7	56
FUC	7	22	3	15
CLI	29	62	3	16
GEN	84	80	6	24
TOB	83	84	6	29
IMI	3,5	13	0	0.5
OFL	0,5	1,5	0	0
VAN	0	0	0	0
MET	29	47	0	0
CIP	0,5	1	0	0

Table 3.9. Comparison of percentage methicillin resistance of MRSA and MRSE isolates over the period 1989 to 1991.

Organism	1989	1990	1991
MRSA	22	29	29
MRSE	43	47	47

Table 3.10. Comparison of percent resistant and intermediate strains of staphylococcal isolates to newer agents.

		1990		1991	
Organism	**Antibiotic**	**R**	**I**	**R**	**I**
MRSA	IMI	0	4	7	13
	OFL	0	0	1	5
	CIP	0	0	1	8
MRSE	IMI	11	6	14	21
	OFL	1	0	2	8
	CIP	0	0	2	8
S. aureus	IMI	0	0	0	0
	OFL	0	0	0	0
	CIP	0	0	0	0
S. epidermidis	IMI	1	0	0	2
	OFL	0	0	0	1
	CIP	0	0	0	1

R = Resistant
I = Intermediate

3.1.3. *ENTEROCOCCUS FAECALIS*

The percentage of resistant isolates of *E. faecalis* from PHPE to a range of antibiotics is presented for the study period 1989 to 1991.

Figures 3.17. and 3.18. present results of annual resistance patterns for the whole hospital and ICU. In 1989, 1990 and 1991, 115, 86 and 94 isolates of *E. faecalis* were recorded for the whole hospital and 23, 13 and 23 for ICU respectively. Figures 3.19. and 3.20. report the mean of percentage resistance for isolates over the period 1989 to 1991 and Table 3.11. presents a comparison of percentage resistance between the whole hospital and the ICU.

A statistical evaluation of the changing patterns of resistance for the whole hospital and ICU is reported in Tables 3.12. and 3.13., respectively.

Over 60% of isolates showed resistance to penicillin and tetracycline for the whole hospital and to penicillin for ICU. Only in the case of ampicillin and piperacillin was the resistance below 10% of isolates. In the comparison of percentage resistance between the whole hospital and the ICU, tetracycline and erythromycin showed a lower resistance in the ICU than that recorded for the whole hospital (Table 3.11.).

The increasing change of percent resistant of *E. faecalis* isolates from the whole hospital and ICU to penicillin and to cotrimoxazole (whole hospital) proved to be statistically significant (Table 3.12., 3.13.).

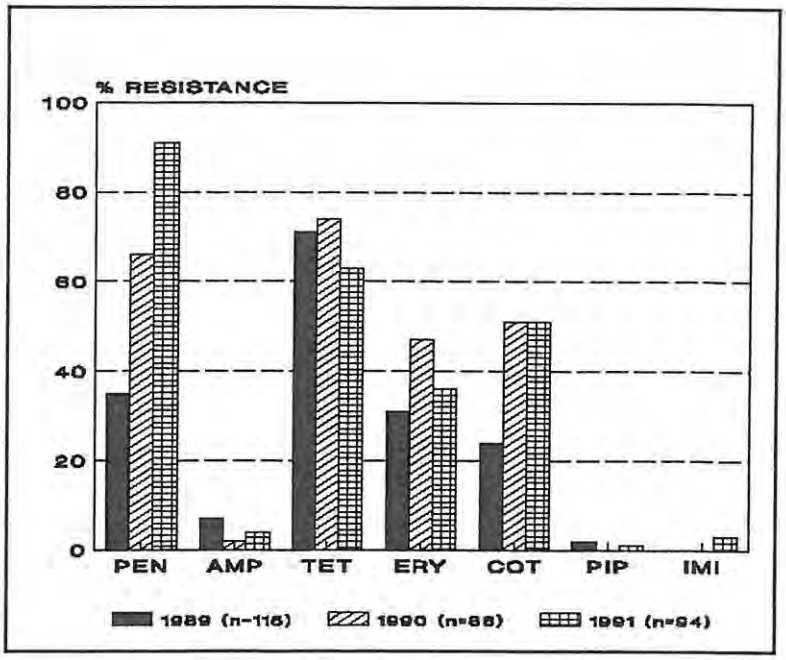

Figure 3.17. Percentage of isolates of *E. faecalis* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

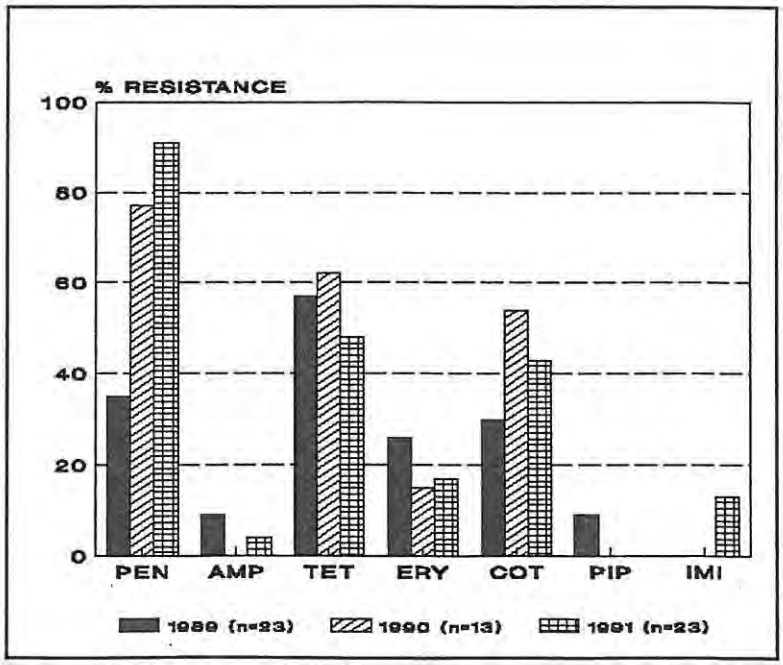

Figure 3.18. Percentage of isolates of *E. faecalis* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

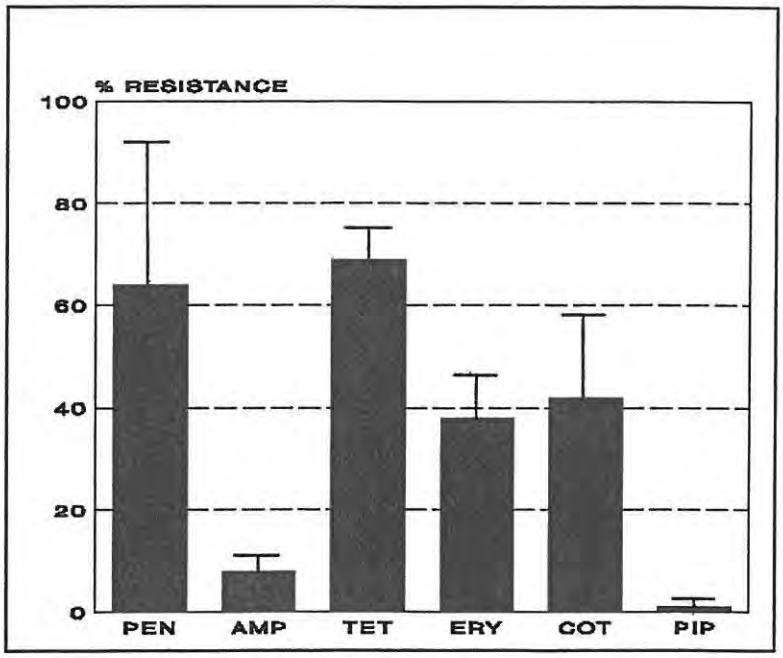

Figure 3.19. The mean of resistant isolates of *E. faecalis* for PHPE (whole hospital). Results reported with one standard deviation.

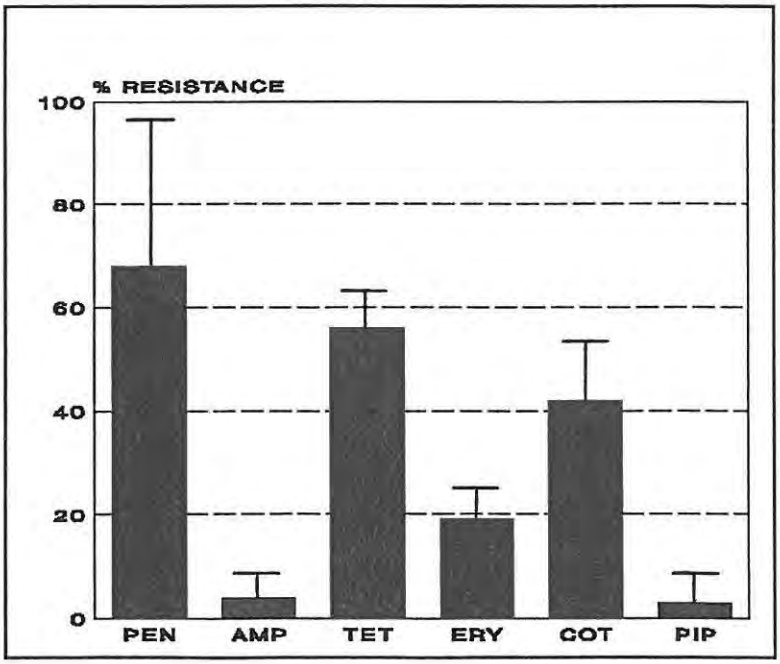

Figure 3.20. The mean of resistant isolates of *E. faecalis* for PHPE (ICU). Results reported with one standard deviation.

Table 3.11. Comparison of percentage resistant isolates of *E. faecalis* between the whole hospital and ICU 1989/1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
AMP	7	9	2	0	4	4
PIP	2	9	0	0	1	0
PEN	35	35	66	77	91	91
TET	71	57	74	62	63	48
COT	24	30	51	54	51	43
ERY	31	26	47	15	36	17
IMI	NT	NT	0	0	3	13

NT = not tested.

Table 3.12. Test for proportions comparing % resistance of *E. faecalis* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	**1989/1990**		**1990/1991**		**1989/1991**	
AMP	1,7744	#	0,7928	#	0,9610	#
PIP	1,5320	#	0,9744	#	0,6022	#
PEN	4,5769	**	4,2375	**	10,4906	**
TET	0,4727	#	1,6016	#	1,2242	#
COT	4,0285	**	0	#	4,1442	**
ERY	2,3199	#	1,5042	#	0,7615	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.13. Test for proportions comparing % resistance of *E. faecalis* isolates in PHPE (ICU) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	1,5082	#	0,9789	#	0,6914	#
PIP	1,5082	#	0	#	1,5082	#
PEN	2,7389	**	1,0680	#	4,8283	**
TET	0,2947	#	0,8225	#	0,6137	#
COT	1,4282	#	0,6376	#	0,9242	#
ERY	0,8160	#	0,1584	#	0,7474	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

3.1.4. *ENTEROCOCCUS FAECIUM*

The percentage of resistant isolates of *E. faecium* from PHPE to a range of six antibiotics is presented for the study period 1989 to 1991.

Figure 3.21. presents results of annual resistance patterns for the whole hospital. In 1989, 1990 and 1991, 14, 15 and 15 isolates of *E. faecium* were recorded.

Figure 3.22 reports the mean of percentage resistance and Table 3.14. presents a statistical evaluation of changing patterns of resistance for the whole hospital. *E. faecium* isolates from the ICU were in 1989 two, 1990, three and 1991, six and too few to present annual resistance and compare with the whole hospital.

Over 40% of isolates showed resistance to penicillin and tetracycline and only in the case of ampicillin, cotrimoxazole and piperacillin was the resistance 20% or below of isolates.

The comparison of the change in resistance patterns over the three year period was made and it was found that resistance of *E. faecium* isolates from the whole hospital to penicillin showed a statistically significant increase.

Table 3.15. presents a comparison of percent resistance for each year of the study period of *E. faecalis* and *E. faecium* and their respective mean resistance percentages. The mean percentage resistance of *E. faecium* is lower than *E. faecalis* except in the case of ampicillin and piperacillin.

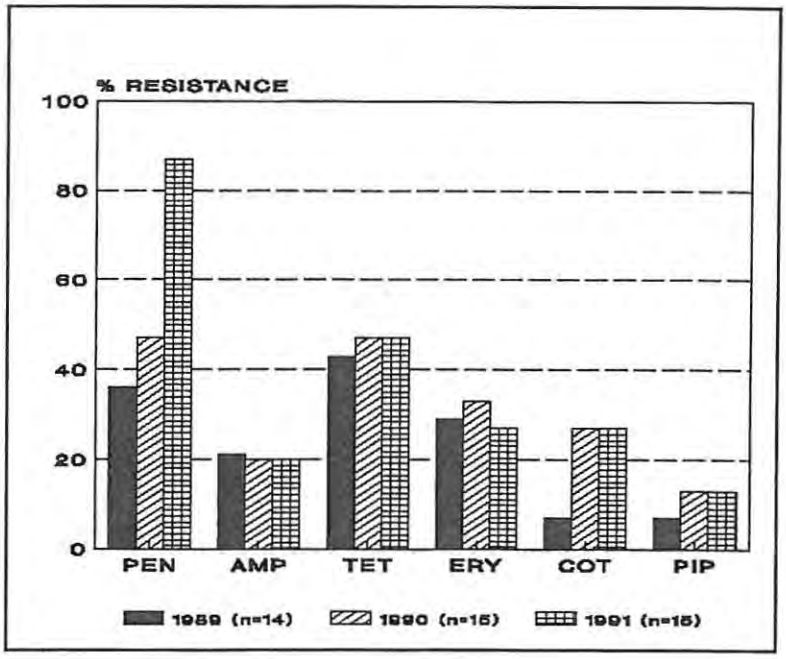

Figure 3.21. Percentage of isolates of *E. faecium* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

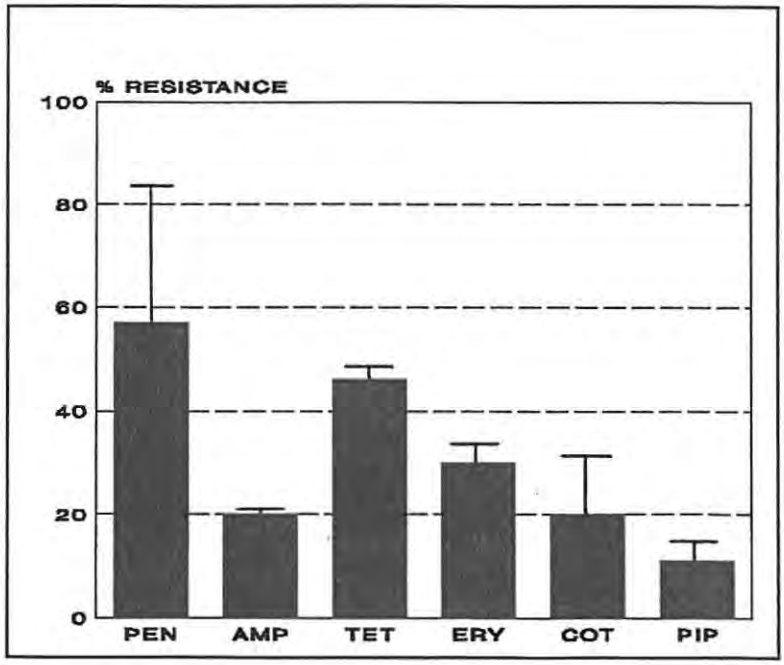

Figure 3.22. The mean of resistant isolates of *E. faecium* for PHPE (whole hospital). Results reported with one standard deviation.

Table 3.14. Test for proportions comparing % resistance of *E. faecium* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	0,0666	#	0	#	0,0666	#
PIP	0,5434	#	0	#	0,5434	#
PEN	0,6049	#	2,5741	**	3,2922	**
TET	0,2166	#	0	#	0	#
COT	1,4995	#	0	#	1,4995	#
ERY	0,2331	#	0,3593	#	0,1199	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.15. A comparison of percent resistance of *E. faecalis* and *E. faecium* isolates in PHPE (whole hospital) for 1989, 1990, 1991 and the mean percentage of the three years.

	1989		1990		1991		MEAN	
Antibiotic	E.faecalis	E.faecium	E.faecalis	E.faecium	E.faecalis	E.faecium	E.faecalis	E.faecium
PEN	35	36	66	47	91	87	64	57
AMP	7	21	2	20	4	20	4	20
TET	71	43	74	47	63	47	69	46
ERY	31	29	47	33	36	27	38	30
COT	24	7	51	27	51	27	42	20
PIP	2	7	0	13	1	13	2	11

3.2. GRAM NEGATIVE BACILLI

3.2.1. *ACINETOBACTER ANITRATUS*

The percentage of resistant isolates of *A. anitratus* from PHPE to a range of fourteen antibiotics is presented for the study period 1989-1991. Figures 3.23. and 3.24. present results of annual resistance patterns for the whole hospital and for the ICU In 1989, 1990 and 1991, 63, 58 and 49 isolates of *A. anitratus* were recorded for the whole hospital and 42, 32 and 33 for ICU respectively.

Figures 3.25. and 3.26. report the mean of percentage resistance for isolates over the period 1989-1991 and Table 3.16 presents a comparison of percentage resistance between the whole hospital and the ICU

Tables 3.17. and 3.18. reports a statistical evaluation of changing patterns of resistance for the whole hospital and ICU respectively and Figure 3.27. shows this change in terms of a monthly percentage resistance pattern.

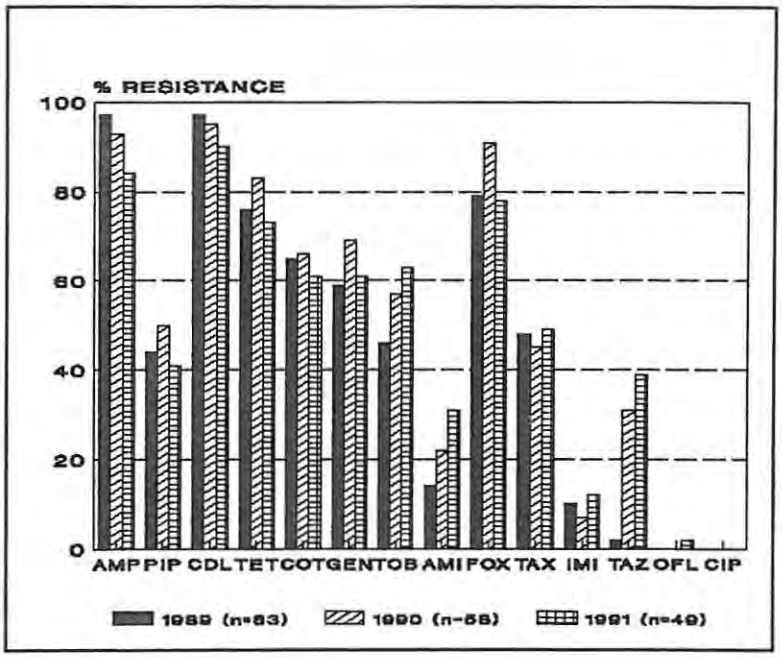

Figure 3.23 Percentage of isolates of *A. anitratus* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

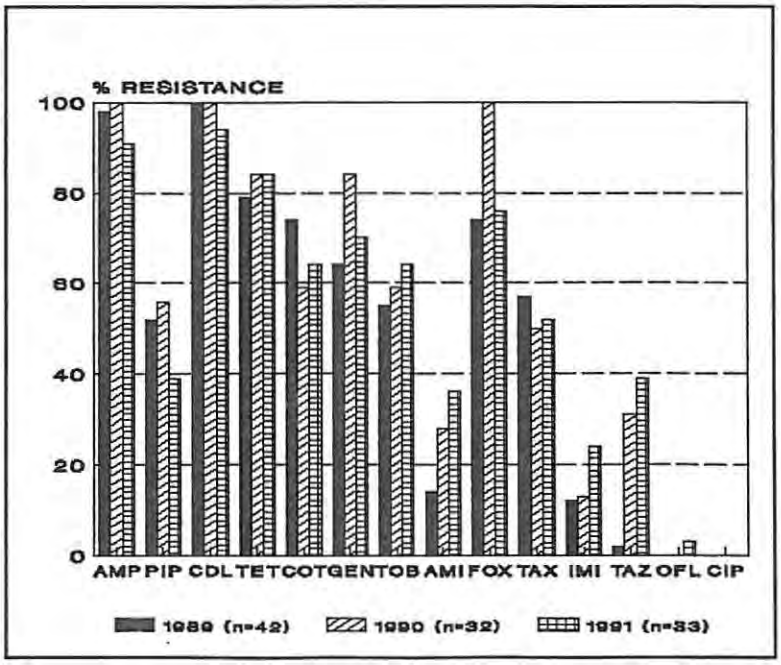

Figure 3.24. Percentage of isolates of *A. anitratus* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

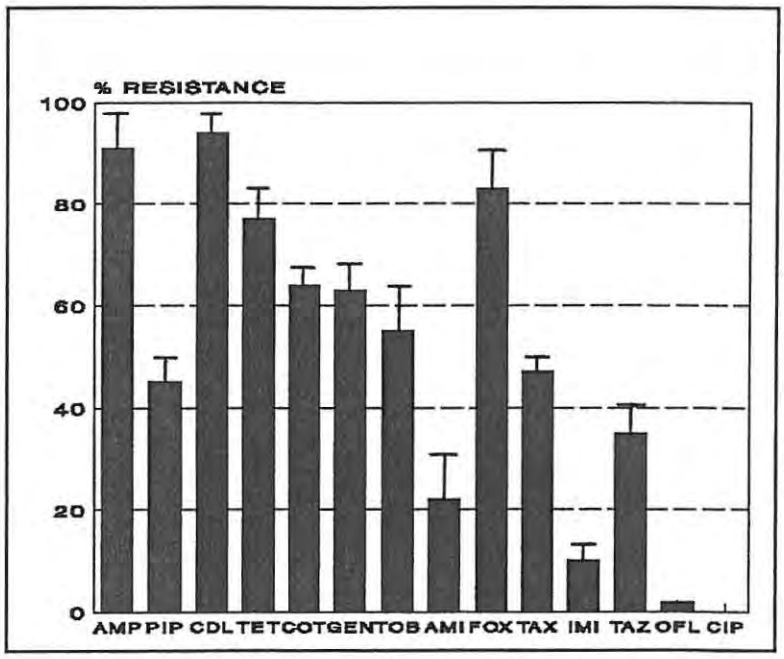

Figure 3.25. The mean of resistant isolates of *A. anitratus* for PHPE (whole hospital). Results reported with one standard deviation.

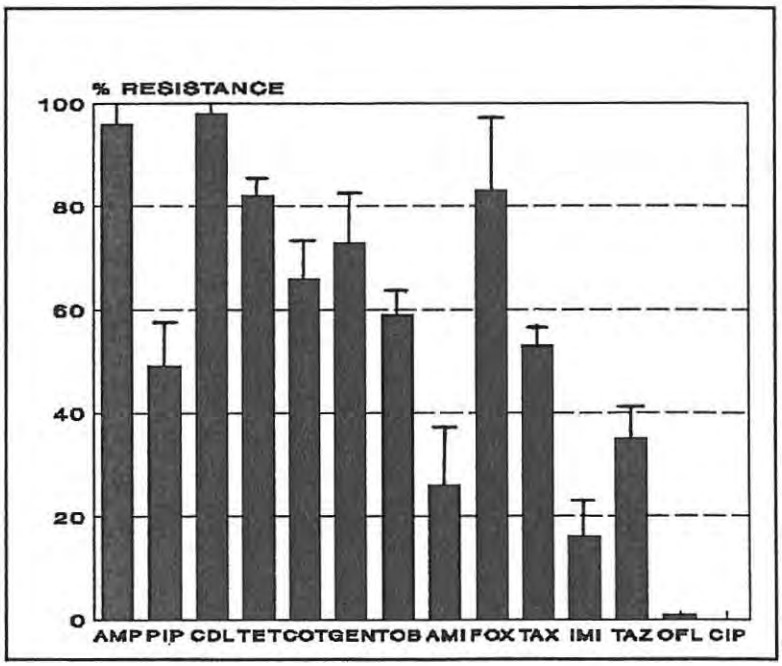

Figure 3.26. The mean of resistant isolates of *A. anitratus* from PHPE (ICU). Results reported with one standard deviation.

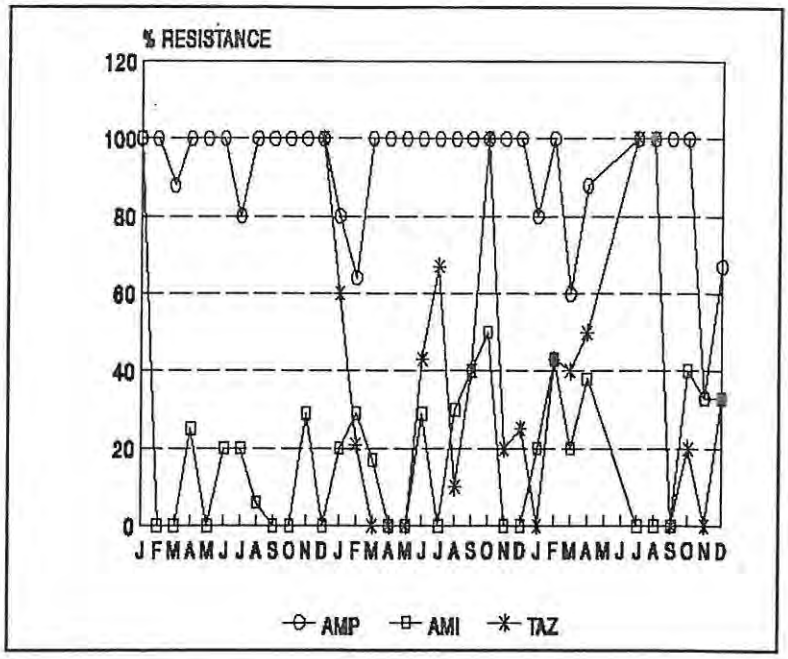

Figure 3.27. Monthly percentage of resistant isolates over the three year period for PHPE (whole hospital) for *A. anitratus* demonstrating a statistically significant change in pattern to ampicillin, amikacin and ceftazidime.

In both the whole hospital and the ICU the number of isolates was found to decrease over each year of the study (Figures 3.23. and 3.24.). The results for the whole hospital and ICU show similar trends, but with resistant isolates occurring in a higher percentage of isolates in the ICU

Over 80% of isolates showed resistance to a penicillin (AMP), second generation cephalosporins (CDL and FOX) and tetracycline. Only in the case of amikacin and imipenem was the resistance below 30% of isolates. However, the trend of increasing resistance to amikacin over the three year period was found to be a statistically significant change. In addition to the above trends, in the ICU over 80% of isolates showed resistance to gentamicin.

In the comparison of percentage resistance between the whole hospital and the ICU, the ICU percentage resistance is higher than that recorded for the whole hospital. The exceptions being:

1989 - Cefoxitin

1990 - Cotrimoxazole

1991 - Piperacillin and cefoxitin

The comparison of the change in resistance patterns over the three year period was made to determine whether any increase or decrease in percent resistance was statistically significant and it was found that resistance of *A. anitratus* isolates from the whole hospital to ampicillin has shown a statistically significant decrease and to amikacin and ceftazidime a statistically significant increase. In the case of the ICU gentamicin, amikacin and ceftazidime showed a pattern of increasing resistance and cefoxitin both an increase (1989 to 1990) and a decrease (1990 to 1991).

Where statistically significant changes were identified the monthly trends were plotted for the whole hospital in order to demonstrate the interval at which the particular change could have been identified for purposes of feedback to the clinical staff.

Table 3.16. Comparison of percentage Resistant isolates of *A. anitratus* between the whole hospital and ICU 1989 - 1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
AMP	97	98	93	100	84	91
PIP	44	52	50	56	41	39
CDL	97	100	95	100	90	94
TET	76	79	83	84	73	84
COT	65	74	66	59	61	64
GEN	59	64	69	84	61	70
TOB	46	55	57	59	63	64
AMI	14	14	22	28	31	36
FOX	79	74	91	100	78	76
TAX	48	57	45	50	49	52
IMI	10	12	7	13	12	24
TAZ	2	2	31	31	39	39
OFL	NT	NT	NT	0	2	3
CIP	NT	NT	NT	0	0	0

NT = not tested

Table 3.17. Test for proportions comparing % resistance of *A. anitratus* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	**1989/1990**		**1990/1991**		**1989/1991**	
AMP	1,0049	#	1,4476	#	2,2964	*
PIP	0,6617	#	0,9359	#	0,3189	#
CDL	0,5588	#	0,9702	#	1,4600	#
TET	0,9590	#	1,2446	#	0,3607	#
COT	0,1156	#	0,5353	#	0,4347	#
GEN	1,1526	#	0,8655	#	0,2144	#
TOB	1,2171	#	0,6331	#	1,8225	#
AMI	1,1464	#	1,0516	#	2,1458	*
FOX	1,8867	#	1,8545	#	0,1277	#
TAX	0,3307	#	0,4137	#	0,1050	#
IMI	0,5940	#	0,8734	#	0,3341	#
TAZ	4,5858	**	0,8655	#	5,1477	**
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

Table 3.18. Test for proportions comparing % resistance of *A. anitratus* isolates in PHPE ICU over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	0,9258	#	1,7225	#	1,2381	#
PIP	0,3425	#	1,3923	#	1,1336	#
CDL	0	#	1,4513	#	1,4513	#
TET	0,5538	#	0	#	0,5582	#
COT	1,3614	#	0,4146	#	0,9300	#
GEN	2,0322	*	1,3621	#	0,5512	#
TOB	0,3449	#	0,4050	#	0,7725	#
AMI	1,4622	#	0,6942	#	2,2169	*
FOX	3,8415	**	3,2282	**	0,1989	#
TAX	0,5992	#	0,1613	#	0,4319	#
IMI	0,1286	#	1,1556	#	1,3382	#
TAZ	3,4294	**	0,6787	#	4,2232	**
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.2. *ENTEROBACTER CLOACAE*

The percentage of resistant isolates of *E. cloacae* from PHPE to a range of antibiotics is presented for the three year study period, 1989 - 1991.

Figures 3.28. and 3.29. present results of annual resistance patterns for the whole hospital and for the ICU. In 1989, 1990 and 1991, 65, 51 and 64 isolates of *E. cloacae* were recorded for the whole hospital and 40, 34 and 36 for the ICU respectively.

Figures 3.30. and 3.31. report the mean of percentage resistance for isolates from PHPE whole hospital and ICU respectively and Table 3.19. presents a comparison of percentage resistance between the whole hospital and the ICU.

Tables 3.20. and 3.21. present a statistical evaluation of changing patterns of resistance for the whole hospital and ICU respectively and Figure 3.32. shows this change for the whole hospital in terms of a monthly percentage resistance pattern.

The results for the whole hospital and ICU show similar trends with the exceptions in the case of piperacillin and cefamandole where the percentage resistant isolates showed an increase from 1989 to 1990, but decreased slightly in 1991 for the whole hospital, whereas in ICU they continued to increase. Over 90% of isolates showed resistance to ampicillin and cefoxitin and over 40% to tetracyclines.

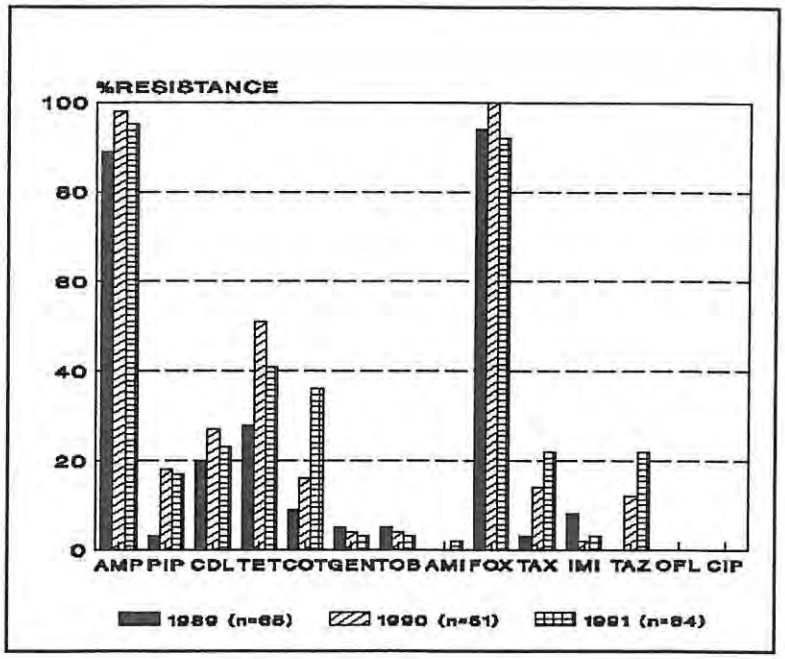

Figure 3.28. Percentage of isolates of *E. cloacae* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

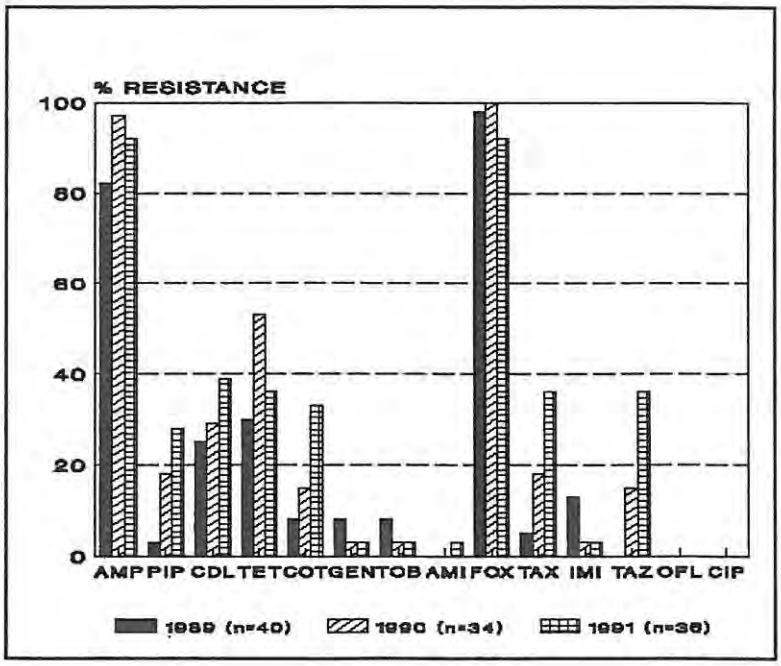

Figure 3.29. Percentage of isolates of *E. cloacae* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

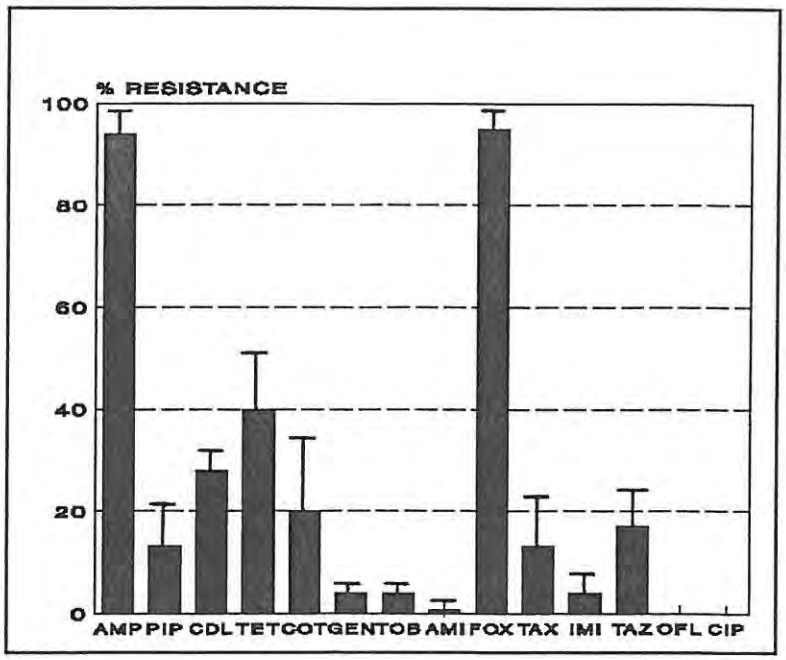

Figure 3.30 The mean of resistant isolates of *E. cloacae* for PHPE (whole hospital). Results reported with one standard deviation.

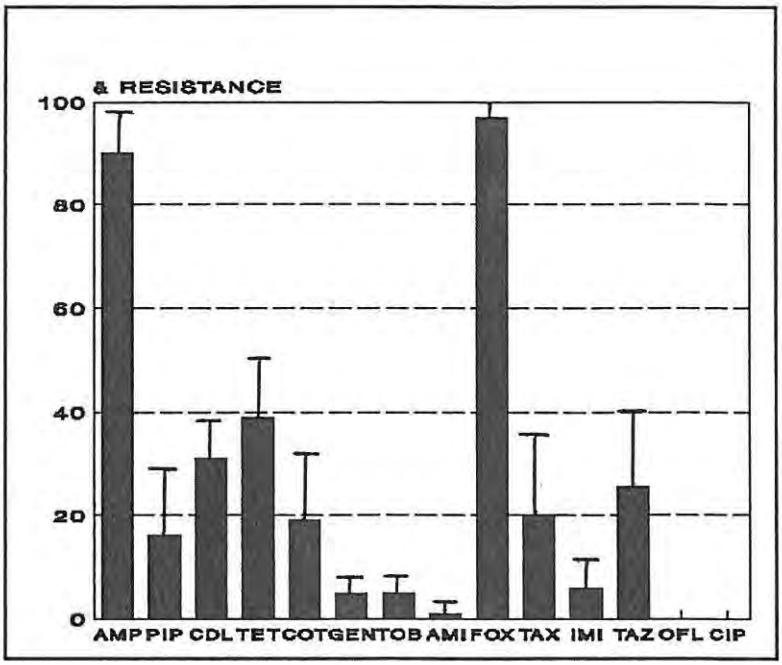

Figure 3.31. The mean of resistant isolates of *E. cloacae* for PHPE (ICU). Results reported with one standard deviation.

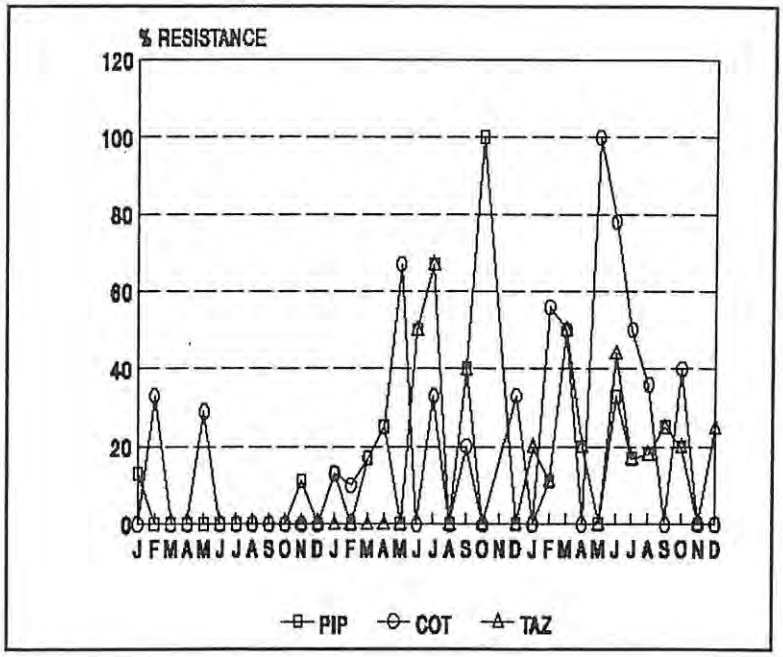

Figure 3.32. Monthly percentage of resistant isolates over the three year period for PHPE (whole hospital) for *E. cloacae* demonstrating a statistically significant change in pattern to piperacillin, cotrimoxazole and ceftazidime.

In the comparison of percentage resistance between the whole hospital and the ICU (Table 3.19.) the ICU percentage resistance is higher in the second and third generation cephalosporins and in 1991 for piperacillin. Ampicillin shows a higher percentage resistance in the whole hospital.

The comparison of the change in resistance patterns over the study period showed that increases in percent resistance of *E. cloacae* to ampicillin, piperacillin, tetracycline, cotrimoxazole, cefoxitin, cefotazime and ceftazidime for the whole hospital, were statistically significant. The decrease is in resistance to cefoxitin for the period 1990 to 1991 was noted and was found to be statistically significant.

In the case of the ICU, ampicillin, piperacillin, tetracycline, cotrimoxazole, cefotazime and ceftazidime all showed a pattern of statistically significant increasing resistance.

The statistically significant changes were identified as mainly occurring in piperacillin, cotrimoxazole and ceftazidime and monthly trends were plotted for the whole hospital in order to attempt to demonstrate an interval at which the occurrence of the particular change could be determined (Figure 3.32.).

Table 3.19. Comparison of percentage resistant isolates of *E. cloacae* between the whole hospital and ICU over the three year period 1989 - 1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
AMP	89	82	98	97	95	92
PIP	3	3	18	18	17	28
CDL	20	25	27	29	23	39
TET	28	30	51	53	41	36
COT	9	8	16	15	36	33
GEN	5	8	4	3	3	3
TOB	5	8	4	3	3	3
AMI	0	0	0	0	2	3
FOX	94	98	100	100	92	92
TAX	3	5	14	18	22	36
TAZ	0	0	12	15	22	36
IMI	8	13	2	3	3	3
OFL	NT	NT	NT	0	0	0
CIP	NT	NT	NT	NT	0	0

NT = not tested

Table 3.20. Test for proportions comparing % resistance of *E. cloacae* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1999/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	2,0699	*	0,8938	#	1,2654	#
PIP	2,5948	**	0,1400	#	2,7184	**
CDL	0,8801	#	0,4912	#	0,4149	#
TET	2,5712	**	1,0733	#	1,5671	#
COT	1,1216	#	2,5328	**	3,8729	**
GEN	0,2596	#	0,2878	#	0,5809	#
TOB	0,2596	#	0,2878	#	0,5809	#
AMI	0	#	1,1429	#	1,1429	#
FOX	2,0368	*	2,3591	**	0,4452	#
TAX	2,0757	*	1,1266	#	3,3967	**
IMI	1,5407	#	0,3452	#	1,2551	#
TAZ	2,6522	**	0,9725	#	4,2487	**
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

Table 3.21. Test for proportions comparing % resistance of *E. cloacae* isolates in PHPE (ICU) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	2,2248	*	0,9284	#	1,3205	#
PIP	2,1069	*	1,0029	#	3,1428	**
CDL	0,3859	#	0,8886	#	1,3173	#
TET	2,0509	*	1,4510	#	0,5559	#
COT	0,9363	#	1,8098	#	2,7983	**
GEN	0,9629	#	0	#	0,9716	#
TOB	0,9629	#	0	#	0,9716	#
AMI	0	#	1,0552	#	1,0552	#
FOX	0,9035	#	1,7693	#	1,1918	#
TAX	1,7484	#	1,7368	#	3,5589	**
IMI	1,6477	#	0	#	1,6584	#
TAZ	2,4495	**	2,0844	*	4,5000	**
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.3. *ESCHERICHIA COLI*

The percentage of resistant isolates of *E. coli* from PHPE to a range of antibiotics is presented for the study period 1989 - 1991.

Figures 3.33. and 3.34. present results of annual resistance patterns for the whole hospital and for the ICU. In 1989, 1990 and 1991, 103, 117 and 132 isolates of *E. coli* were recorded for the whole hospital and 22, 24 and 33 for the ICU respectively.

Figures 3.35. and 3.36. report the mean of percentage resistance for isolates over the period 1989 - 1991 and Table 3.22. presents a comparison of percentage resistance between the whole hospital and ICU. Tables 3.23. and 3.24. report a statistical evaluation of changing patterns of resistance for the whole hospital and ICU respectively.

The number of isolates was found to increase over each year of the study in both the whole hospital and the ICU (Figures 3.33. and 3.34.). The results for the whole hospital and ICU both showed three peaks in percentage resistance to ampicillin, tetracycline and cotrimoxazole with over 60% of isolates showing resistance to ampicillin and cotrimoxazole. Except for piperacillin, the resistance to all other agents was below 20 percent of isolates. In both the whole hospital and ICU the resistance of isolates to piperacillin and cefoxitin peaked in 1990.

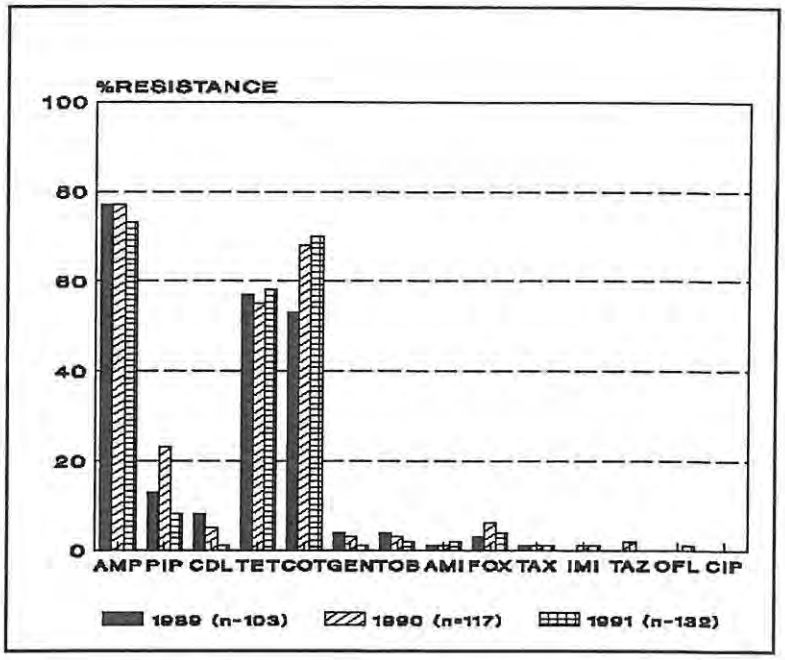

Figure 3.33. Percentage of isolates of *E. coli* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

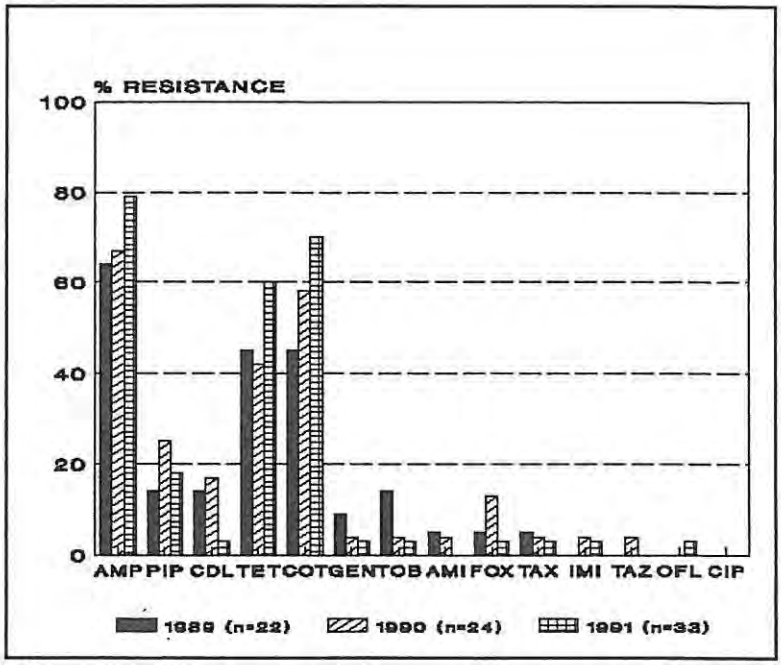

Figure 3.34. Percentage of isolates of *E. coli* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989- 1991.

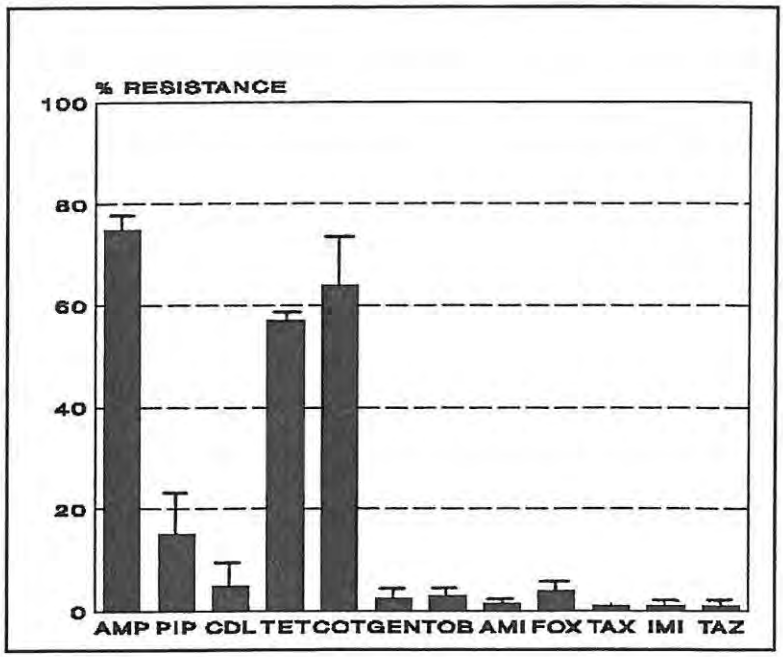

Figure 3.35. The mean of resistaqnt isolates of *E. coli* for PHPE (whole hospital). Results reported with one standard deviation.

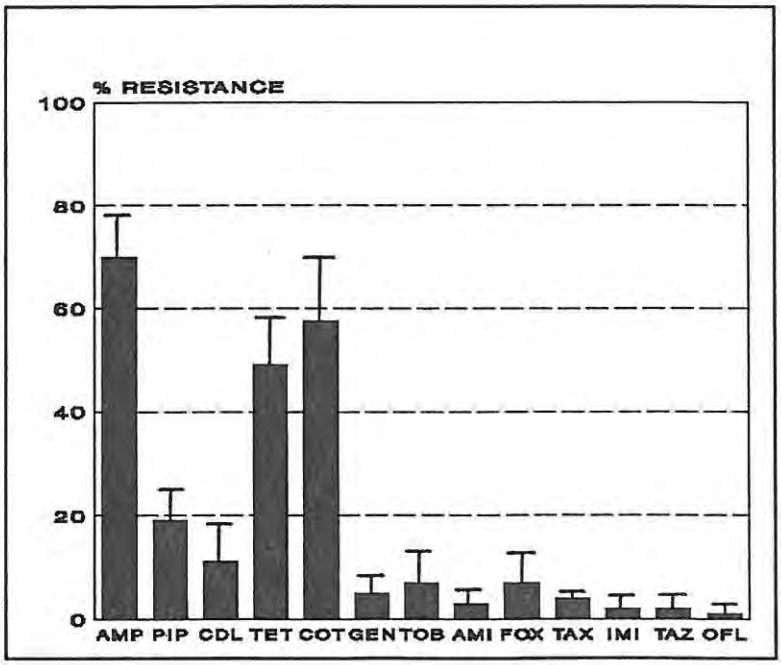

Figure 3.36. The mean of resistant isolates of *E. coli* for PHPE (ICU). Results reported with one standard deviation.

Table 3.22. Comparison of percentage resistant isolates of *E. coli* between the whole hospital and ICU over the three year period 1989 - 1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
AMP	77	64	77	67	73	79
PIP	13	14	23	25	8	18
CDL	8	14	5	17	1	3
TET	57	45	55	42	58	60
COT	53	45	68	58	70	70
GEN	4	9	3	4	1	3
TOB	4	14	3	4	2	3
AMI	1	5	1	4	2	0
FOX	3	5	6	13	4	3
TAX	1	5	1	4	1	3
TAZ	0	0	2	4	0	0
IMI	0	0	1	4	1	3
OFL	NT	NT	NT	0	1	3
CIP	NT	NT	NT	NT	0	0

NT = not tested

In the comparison of percentage resistance between the whole hospital and the ICU (Table 3.22.), the ICU percentage resistance is higher than that recorded for the whole hospital. The exceptions being ampicillin, tetracycline and cotrimoxazole in 1989 and 1990, and amikacin in 1991.

The statistically significant changes in resistance patterns were compared for the three year study period and identified for the whole hospital (Table 3.23.). Piperacillin showed both an increase in percentage resistance (1989 - 1990) and a decrease (1990 - 1991). Cefamandole demonstrated a decrease and cotrimoxazole, an increase in percentage resistance over the three years. In the ICU, none of the changes proved to be statistically significant (Table 3.24.).

Table 3.23. Test for proportions comparing % resistance of *E. coli* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	0	#	0,7294	#	0,7057	#
PIP	1,9568	*	3,2959	**	1,2288	#
CDL	0,8962	#	1,8239	#	2,4912	**
TET	0,2983	#	0,4767	#	0,1538	#
COT	2,2933	*	0,3404	#	2,6848	**
GEN	0,4011	#	1,1116	#	1,4177	#
TOB	0,4011	#	1,1116	#	1,4177	#
AMI	0	#	0,6550	#	0,6394	#
FOX	1,0850	#	0,7194	#	0,4176	#
TAX	0	#	0	#	0	#
IMI	1,0871	#	0	#	1,1547	#
TAZ	1,5452	#	1,5452	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.24. Test for proportions comparing % resistance of *E. coli* isolates in PHPE (ICU) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	0,2138	#	1,0056	#	1,2048	#
PIP	0,9544	#	0,6315	#	0,4011	#
CDL	0,2816	#	1,7026	#	1,3799	#
TET	0,2051	#	1,3637	#	1,1021	#
COT	0,8887	#	0,9338	#	1,8837	#
GEN	0,6853	#	0,2007	#	0,8842	#
TOB	1,1890	#	0,2007	#	1,3799	#
AMI	0,1631	#	1,000	#	1,0761	#
FOX	0,9651	#	1,3370	#	0,3627	#
TAX	0,1631	#	0,2007	#	0,3627	#
IMI	1,000	#	0,2007	#	1,0103	#
TAZ	1,000	#	1,000	#	0	#
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.3.1. *ESCHERICHIA COLI* ISOLATES FROM URINE SPECIMENS

Figures 3.37. and 3.38. present results of annual resistance patterns for the whole hospital for the period 1989 to 1991 and for OPD for 1990 and 1991.

The number of isolates of *E. coli* recorded from both the whole hospital and OPD was found to decrease over each year of the study. Results for the whole hospital and OPD show similar trends but with resistant isolates occurring in a higher percentage of isolates in the whole hospital.

Over 60% of isolates showed resistance to ampicillin, cotrimoxazole and sulphonamides and in the case of nalidixic acid, nitrofurantoin and nicene, the resistance was below 12% of isolates.

In the comparison of percentage resistance between the whole hospital and OPD, the whole hospital percentage resistance is higher or equal to in all instances than that recorded for OPD (Table 3.25.).

The comparison of the change in resistance patterns was made to determine whether any increase or decrease in percent resistance was statistically significant and it was found that resistance of *E. coli* isolates from the whole hospital to cotrimoxazole and sulphonamides showed a statistically significant increase and to Nicene, a statistically significant decrease (Table 3.26.). Table 3.27. reports a statistical evaluation for OPD and shows that the changes were not significant.

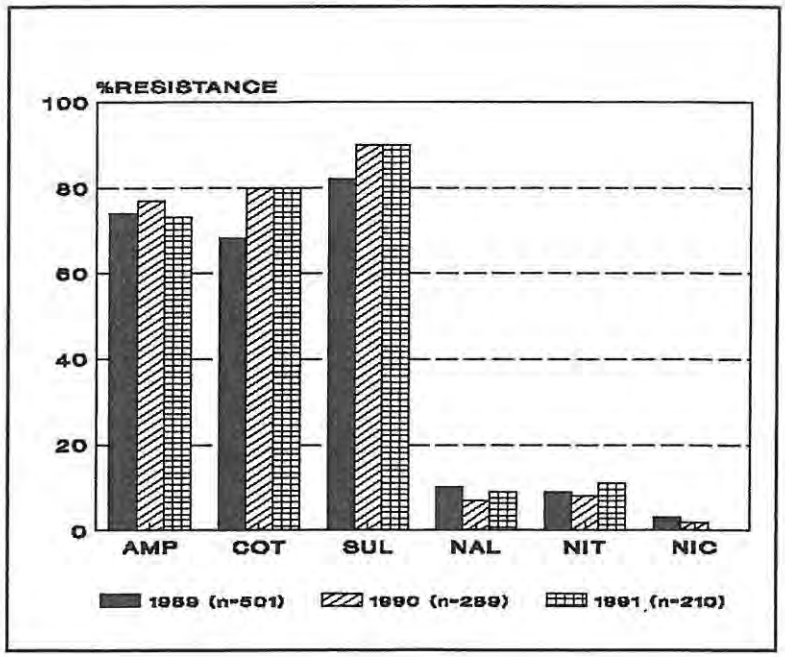

Figure 3.37. Percentage of isolates from urine specimens of *E. coli* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 189-1991.

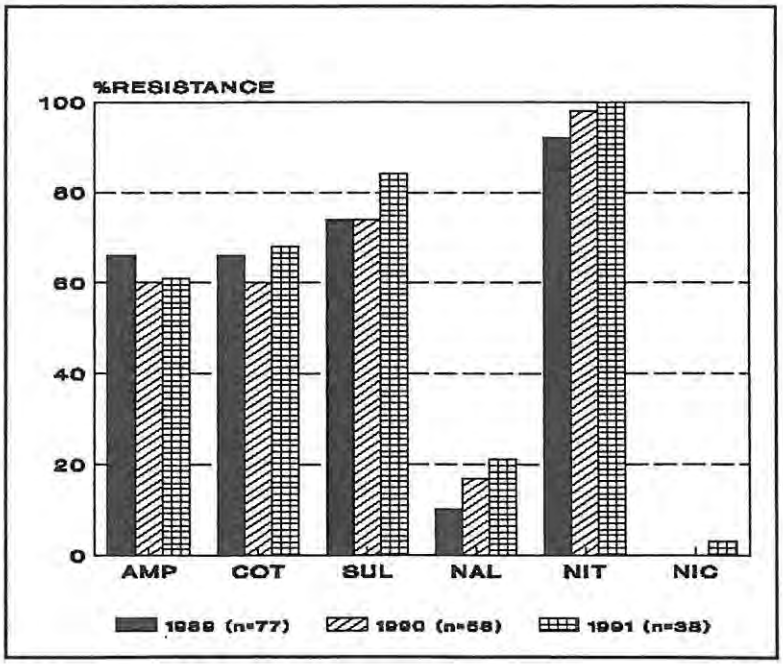

Figure 3.38. Percentage of isolates from urine specimens of *E. coli* from PHPE (OPD) showing resistance to a range of antibiotics over the two year period 1990-1991.

Table 3.25. Comparison of percentage resistant isolates of *E. coli* between the whole hospital and OPD over the three year period 1989-1991.

	1989	1990		1991	
Antibiotic	**Hosp**	**Hosp**	**OPD**	**Hosp**	**OPD**
AMP	74	77	60	73	65
COT	68	80	62	80	71
SUL	82	90	82	90	90
NAL	10	7	8	9	3
NIT	9	8	3	11	8
NIC	3	2	2	0	0

Table 3.26. Test for proportions comparing % resistance of *E. coli* (urine) isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	**1989/1990**		**1990/1991**		**1989/1991**	
AMP	0,9502	#	1,0156	#	0,2750	#
COT	3,8178	**	0	#	3,4695	**
SUL	3,2497	**	0	#	2,9749	**
NAL	1,4909	#	0,8063	#	0,4190	#
NIT	0,4890	#	1,1174	#	0,7970	#
NIC	0,8912	#	2,4286	**	3,9363	**

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.27. Test for proportions comparing % resistance of *E. coli* (urine) isolates in PHPE (OPD) over the period 1990/1991.

Antibiotic	**1990/1991**	
AMP	0,6949	#
COT	1,1525	#
SUL	1,6031	#
NAL	1,5635	#
NIT	1,4048	#
NIC	1,5584	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

3.2.4. *KLEBSIELLA AEROGENES*

The percentage of resistant isolates of *K. aerogenes* from PHPE to a range of fourteen antibiotics is presented for the three year period 1989 to 1991.

Figures 3.39. and 3.40. present results of annual resistance patterns for the whole hospital and for the ICU. In 1989, 1990 and 1991, 88, 57 and 69 isolates of *K. aerogenes* were recorded for the whole hospital and 32, 27 and 35 for ICU respectively. Figures 3.41. and 3.42. report the mean of percentage resistance for isolates over the period 1989 - 1991 and Table 3.28. presents a comparison of percentage resistance between the whole hospital and the ICU. Tables 3.29 and 3.30. present the statistical evaluations of changing patterns of resistance for the whole hospital and ICU respectively.

The results for the whole hospital and ICU show similar trends with an exception being found in cotrimoxazole where in 1989 the percentage resistance was 57% in the whole hospital and 41% in ICU. (Figures 3.39. and 3.40.). Over 90% of isolates showed resistance to ampicillin and 50% and over to tetracycline and cotrimoxazole for the whole hospital and ICU. A percentage resistance for *K. aerogenes* isolates of between 28 and 30 percent is reported for the whole hospital and ICU to gentamicin and tobramycin (Figures 3.41. and 3.42.).

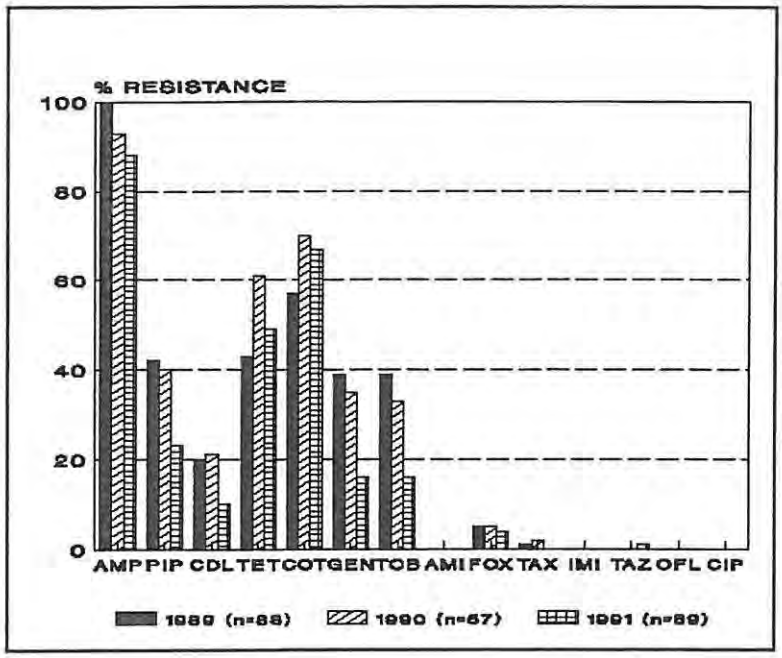

Figure 3.39. Percentage of isolates of *K. aerogenes* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

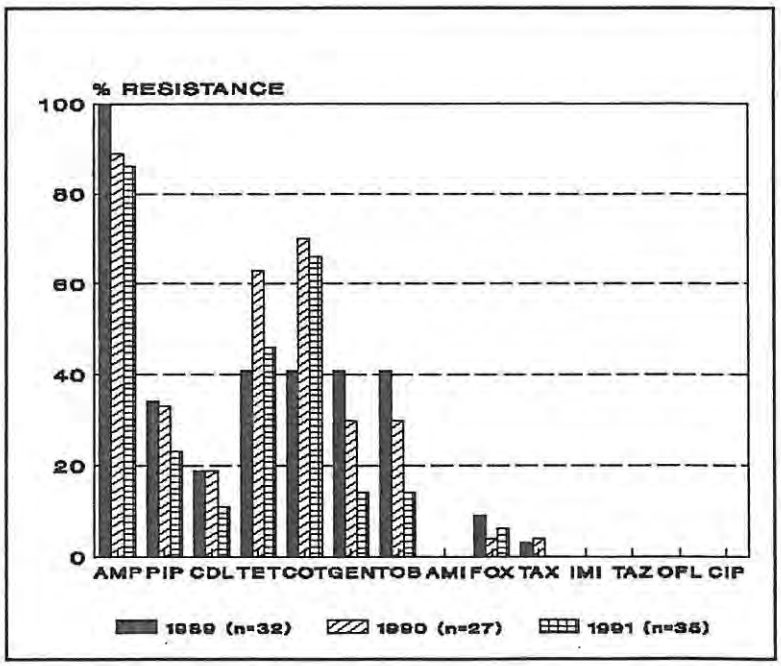

Figure 3.40. Percentage of isolates of *K. aerogenes* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

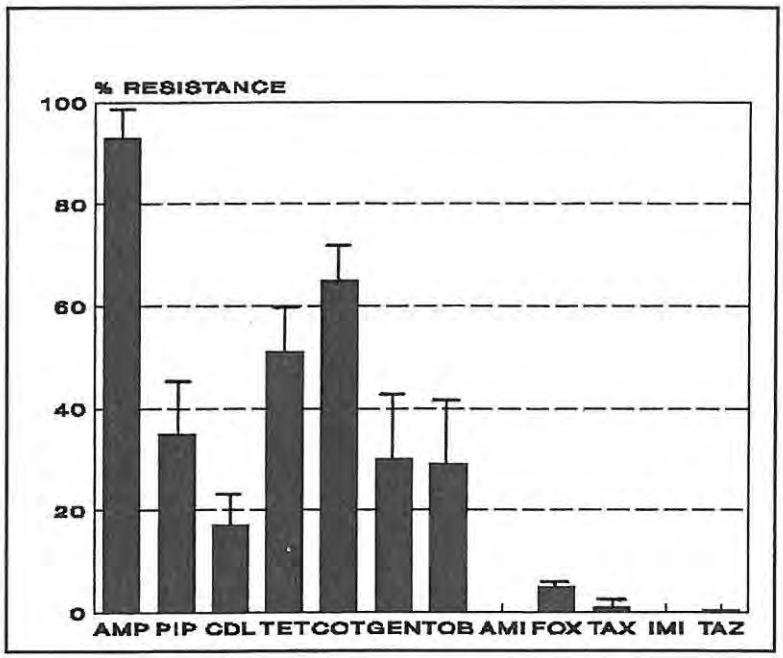

Figure 3.41. The mean of resistant isolates of *K. aerogenes* for PHPE (whole hospital). Results reported with one standard deviation.

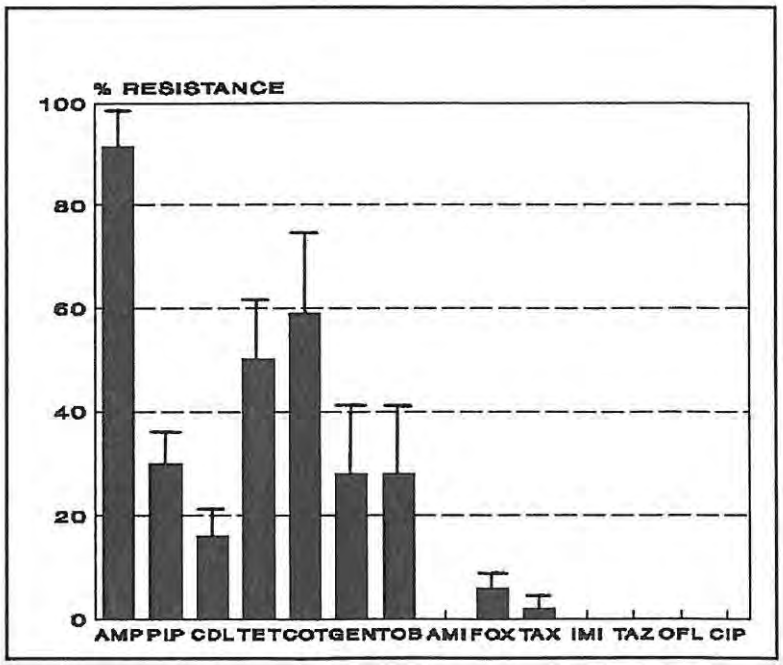

Figure 3.42. The mean of resistant isolates of *K. aerogenes* for PHPE (ICU). Results reported with one standard deviation.

In the comparison of percentage resistance between the whole hospital and the ICU (Table 3.28.) the ICU percentage resistance is lower than that recorded for the whole hospital in the majority of instances; where it is higher, it is only marginally so.

The comparison of the change in resistance patterns over the three year period was made to determine whether any increase or decrease in percent resistance was statistically significant and it was found that resistance of *K. aerogenes* isolates from the whole hospital to ampicillin, piperacillin, gentamicin and tobramycin have shown a statistically significant decrease and an increase in tetracycline (1989 to 1990). In the case of the ICU, ampicillin, gentamicin and tobramycin showed a pattern of decreasing resistance and cotrimoxazole an increase 1989 to 1990 and 1989 to 1991 that were all statistically significant.

Table 3.28. Comparison of percentage resistant isolates of *K. aerogenes* between the whole hospital and ICU over the three year period 1989-1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
AMP	100	100	93	89	88	86
PIP	42	34	40	33	23	23
CDL	20	19	21	19	10	11
TET	43	41	61	63	49	46
COT	57	41	70	70	67	66
GEN	39	41	35	30	16	14
TOB	39	41	33	30	16	14
AMI	0	0	0	0	0	0
FOX	5	9	5	4	4	6
TAX	1	3	2	4	0	0
TAZ	0	0	0	0	1	0
IMI	0	0	0	0	0	0
OFL	NT	NT	NT	0	0	0
CIP	NT	NT	NT	NT	0	0

NT = not tested

Table 3.29. Test for proportions comparing % resistance of *K. aerogenes* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	2,0713	*	0,9672	#	3,0674	**
PIP	0,2394	#	2,0650	*	2,6013	**
CDL	0,1454	#	1,6943	#	1,7896	#
TET	2,1578	*	1,3591	#	0,7496	#
COT	1,6163	#	0,3615	#	1,2921	#
GEN	0,4889	#	2,4654	**	3,3724	**
TOB	0,7395	#	2,2271	*	3,3724	**
AMI	0	#	0	#	0	#
FOX	0	#	0,2682	#	0,3020	#
TAX	0,4681	#	1,0785	#	0,9428	#
IMI	0	#	0	#	0	#
TAZ	0	#	0,8348	#	0,8348	#
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

Table 3.30. Test for proportions comparing % resistance of *K. aerogenes* isolates in PHPE (ICU) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	1,3268	#	0.3569	#	2,3870	**
PIP	0,0814	#	0,8688	#	1,001	#
CDL	0	#	0,8678	#	0,9173	#
TET	1,7289	#	1,3554	#	0,4130	#
COT	2,3417	**	0,3358	#	2,1151	*
GEN	0,8882	#	1,5107	#	2,5744	**
TOB	0,8882	#	1,5107	#	2,5744	**
AMI	0	#	0	#	0	#
FOX	0,7924	#	0,3631	#	0,4645	#
TAX	0,2071	#	1,0607	#	0,9948	#
IMI	0	#	0	#	0	#
TAZ	0	#	0	#	0	#
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.5. *PROTEUS MIRABILIS*

The percentage of resistant isolates of *P. mirabilis* from PHPE to a range of antibiotics is presented for the three year study period, 1989 to 1991.

Figures 3.43. and 3.44. present results of annual resistance patterns for the whole hospital and the ICU. In 1989, 1990 and 1991, 170, 134 and 147 isolates of *P. mirabilis* were recorded for the whole hospital and 47, 37 and 42 for the ICU respectively.

Figures 3.45. and 3.46. report the mean of percentage resistance for isolates from PHPE, whole hospital and ICU respectively and Table 3.31. presents a comparison of percentage resistance between the whole hospital and the ICU. Tables 3.32. and 3.33. report a statistical evaluation of changing patterns of resistance for the whole hospital and ICU respectively.

The results for the whole hospital and ICU both showed two peaks in percentage resistance to ampicillin and cotrimoxazole with the ICU isolates being 16 and 12 percent lower respectively than for the whole hospital. In the ICU the trend of decreasing resistance to cotrimoxazole over the three year period was found to be a statistically significant change. The resistance to all other agents was below 14 percent of isolates for both the whole hospital and the ICU.

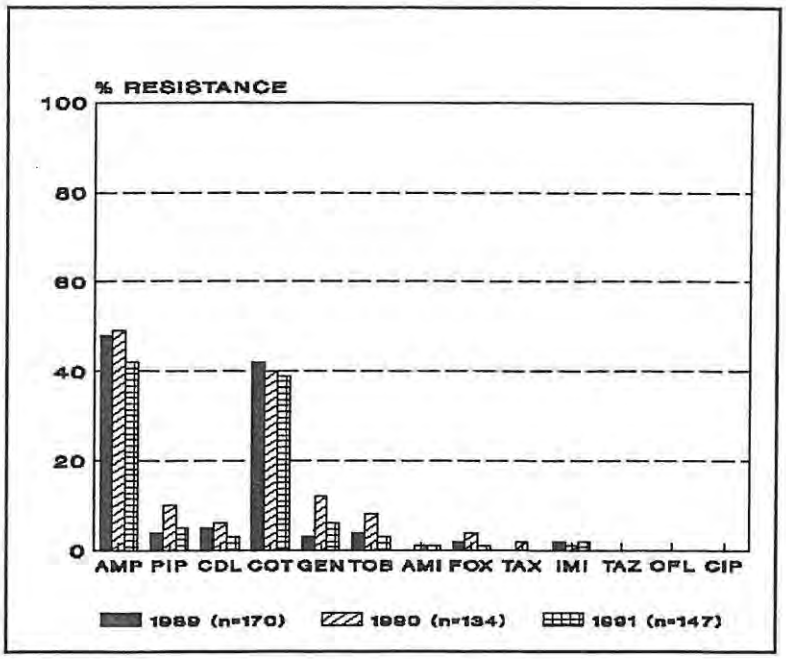

Figure 3.43. Percentage of isolates of *P. mirabilis* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

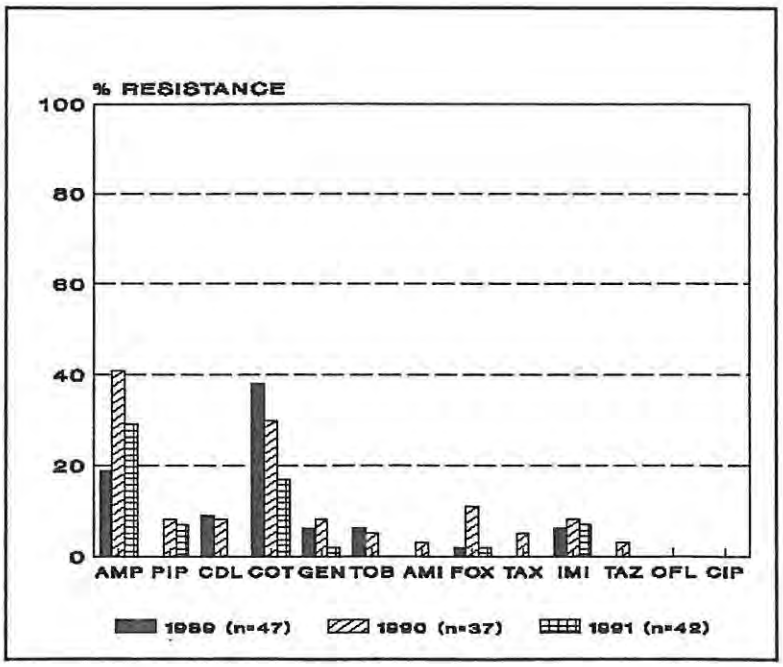

Figure 3.44. Percentage of isoaltes of *P. mirabilis* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

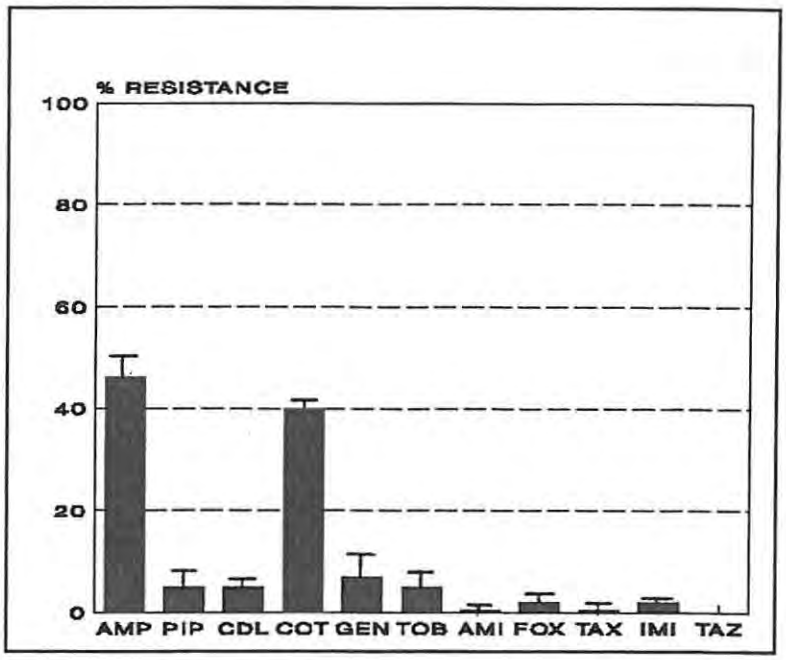

Figure 3.45. The mean of resistant isolates of *P. mirabilis* for PHPE (whole hospital). Results reported with one standard deviation.

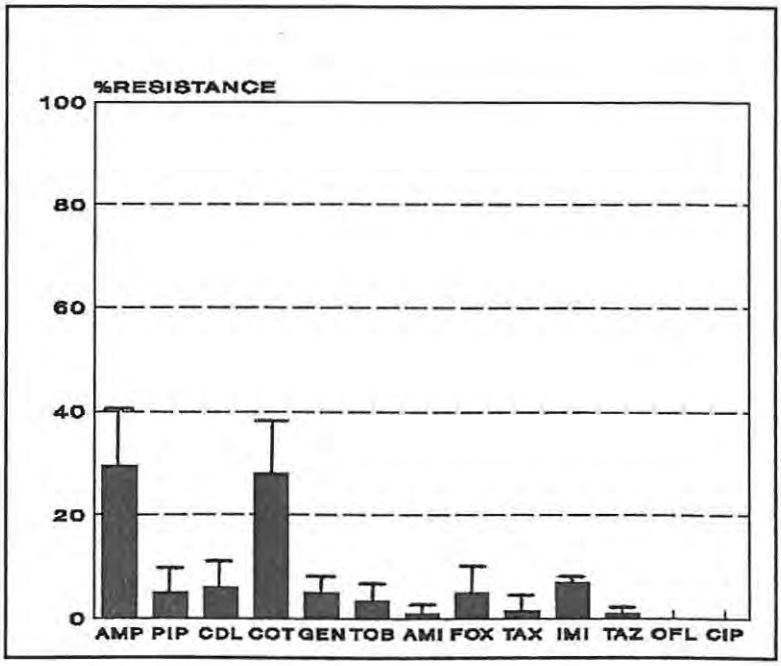

Figure 3.46. The mean of resistant isolates of *P. mirabilis* for PHPE (ICU). Results reported with one standard deviation.

Table 3.31. Comparison of percentage resistant isolates of *P. mirabilis* between the whole hospital and ICU over the three year period 1989-1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
AMP	48	19	49	41	42	29
PIP	4	0	10	8	5	7
CDL	5	9	6	8	3	0
TET	100	100	100	100	100	100
COT	42	38	40	30	39	17
GEN	3	6	12	18	6	2
TOB	4	6	8	5	3	0
AMI	0	0	1	3	1	0
FOX	2	2	4	11	1	2
TAX	0	0	2	5	1	0
TAZ	0	0	0	3	0	0
IMI	2	6	1	8	2	7
OFL	NT	NT	NT	0	0	0
CIP	NT	NT	NT	NT	0	0

NT = not tested

In the comparison between the whole hospital and the ICU, the majority of percentage resistance was lower in the ICU especially ampicillin and cotrimoxazole. However, in the case of imipenem, the ICU percentage resistance was higher (Table 3.31.).

The comparison of the change in resistance patterns over the study period showed that increases in percent resistance of *P. mirabilis* to piperacillin and gentamicin for the whole hospital were statistically significant. In the ICU, ampicillin showed an increase (1989 to 1990) and cefamandole and cotrimoxazole a decrease (1989 to 1991) of statistical significance.

Table 3.32. Test for proportions comparing % resistance of *P. mirabilis* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	0,1732	#	1,1795	#	1,0732	##
PIP	2,0028	*	1,5853	#	0,4268	#
CDL	0,3779	#	1,2059	#	0,9158	#
TET	0	#	0	#	0	#
COT	0,3522	#	0,1713	#	0,5431	#
GEN	2,9059	**	1,7528	#	1,2736	#
TOB	1,4367	#	1,8291	#	0,4857	#
AMI	1,1634	#	0	#	1,2185	#
FOX	0,9977	#	1,5947	#	0,7399	#
TAX	1,6537	#	1,6537	#	0	#
IMI	0,7271	#	0,6947	#	0	#
TAZ	0	#	0	#	0	#
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

Table 3.33. Test for proportions comparing % resistance of *P. mirabilis* isolates in PHPE (ICU) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	2,2209	*	1,1219	#	1,1059	#
PIP	1,7937	#	0,1681	#	1,7780	#
CDL	0,1637	#	1,7937	#	2,1560	*
COT	0,7738	#	1,3676	#	2,2951	*
GEN	0,3542	#	1,2107	#	0,9798	#
TOB	0,2007	#	1,3955	#	1,7321	#
AMI	1,0697	#	1,0697	#	0	#
FOX	1,6262	#	1,6132	#	0	#
TAX	1,3955	#	1,3955	#	0	#
IMI	0,3542	#	0,1681	#	0,1907	#
TAZ	1,0697	#	1,0697	#	0	#
OFL	NT	#	0	#	0	#
CIP	NT	#	0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.5.1. *PROTEUS MIRABILIS* ISOLATES FROM URINE SPECIMENS

Figures 3.47. and 3.48. present results of annual resistance patterns for the whole hospital for the period 1989 to 1991 and for OPD for 1990 and 1991.

The number of isolates of *P. mirabilis* recorded from both the whole hospital and OPD was found to decrease over the study period. In 1989, 1990 and 1991, 77, 58 and 38 isolates were recorded from the whole hospital and in 1990 and 1991, 14 and 6 from OPD respectively.

Only in the case of nalidixic acid and nicene was the percentage resistance below 22% and 5% respectively. In the comparison of percentage resistance between the whole hospital and OPD, the results recorded were very similar for 1990. However, in 1991, the OPD isolates showed a higher percentage resistance than the whole hospital to ampicillin, cotrimoxazole and sulphonamides. (Table 3.34.)

Tables 3.35. and 3.36. present a statistical evaluation of the change in resistance patterns. The increases in percent resistance to nitrofuratoin for the whole hospital and to cotrimoxazole for OPD proved to be statistically significant.

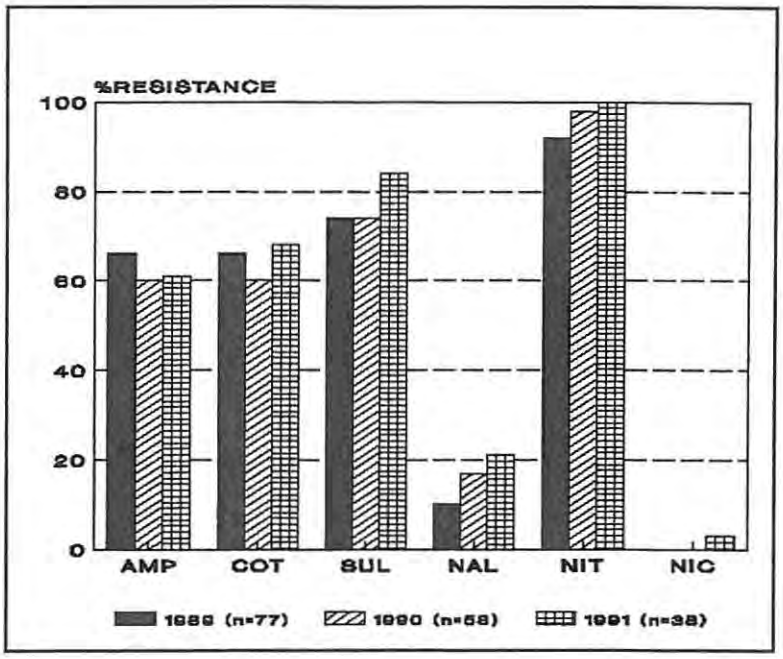

Figure 3.47. Percentage of isolates from urine specimens of *P. mirabilis* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

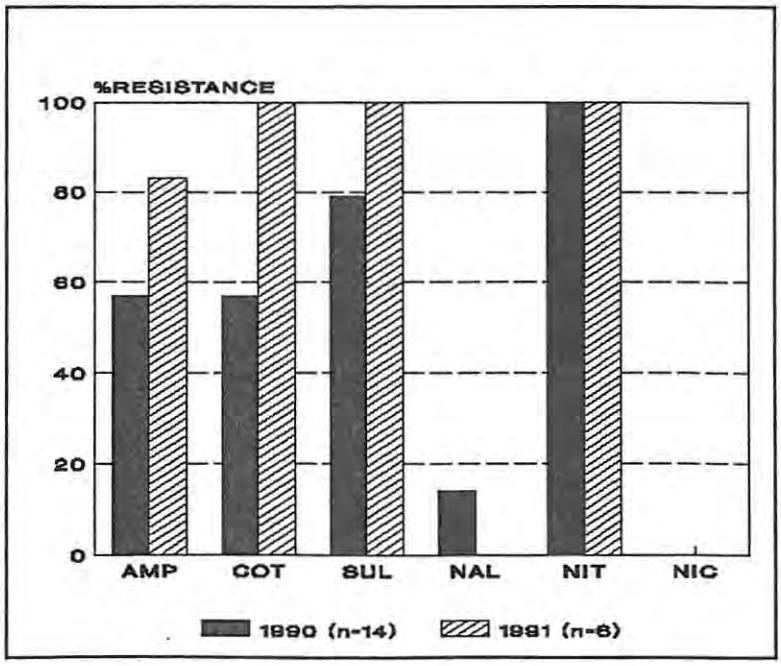

Figure 3.48. Percentage of isolates from urine specimens for *P. mirabilis* from PHPE (OPD) showing resistance to a range of antibiotics over the two year period 1990-1991.

Table 3.34. Comparison of percentage resistant (urine) isolates of *P. mirabilis* between the whole hospital and OPD over the three year period 1989-1991.

	1989	1990		1991	
Antibiotic	**Hosp**	**Hosp**	**OPD**	**Hosp**	**OPD**
AMP	66	60	57	61	83
COT	66	60	57	68	100
SUL	74	74	79	84	100
NAL	10	17	14	21	0
NIT	92	98	100	100	100
NIC	0	0	0	3	0

Table 3.35. Test for proportions comparing % resistance of *P. mirabilis* (urine) isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	**1989/1990**		**1990/1991**		**1989/1991**	
AMP	0,7145	#	0,0981	#	0,5220	#
COT	0,7145	#	0,8055	#	0,2152	#
SUL	0	#	1,2079	#	1,2872	#
NAL	1,1664	#	0,4851	#	1,4786	#
NIT	1,6681	#	1,0880	#	2,5876	**
NIC	0	#	1,0841	#	1,0841	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.36. Test for proportions comparing % resistance of *P. mirabilis* (urine) isolates in PHPE (OPD) over the period 1990/1991.

Antibiotic	**1990/1991**	
AMP	1,2837	#
COT	3,2498	**
SUL	1,9291	#
NAL	1,5097	#
NIT	0	#
NIC	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

3.2.6. *PSEUDOMONAS AERUGINOSA*

The percentage of resistant isolates of *P. aeruginosa* from PHPE to a range of eight antibiotics is presented for the study period 1989 to 1991.

Figures 3.49. and 3.50. report results of annual resistance patterns for the whole hospital and ICU. In 1989, 1990 and 1991, 176, 134 and 150 isolates of *P. aeruginosa* were recorded for the whole hospital and 70, 68 and 77 for ICU respectively. Figures 3.51. and 3.52. present the mean of percentage resistance for isolates over the period 1989 - 1991 and Table 3.37. reports a comparison of percentage resistance between the whole hospital and the ICU. Tables 3.38. and 3.39. report a statistical evaluation of changing patterns of resistance for the whole hospital and ICU.

In the whole hospital *P. aeruginosa* isolates showed percentage resistance of 10 percent and under to all antibiotics tested except for imipenem which peaked in 1990 to 18 percent. The increase of resistance 1989 to 1990 was found to be a statistically significant change. This peak is also found in the ICU with imipenem but at almost double the percentage resistance. Ciprofloxacin and ofloxacin, tested against this organism only in 1991, were recorded as 5 and 7 percent resistance respectively for the whole hospital and 6 and 12 percent resistance respectively for the ICU.

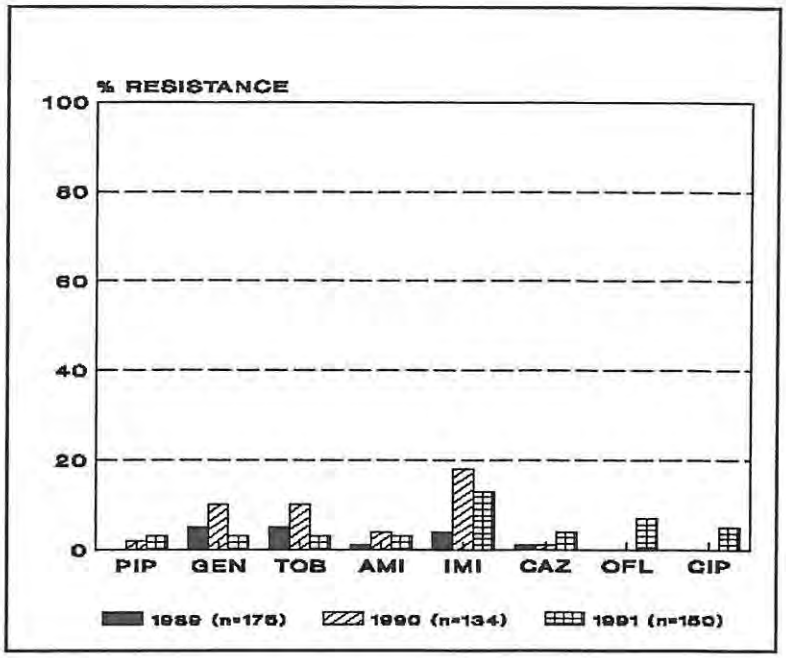

Figure 3.49. Percentage of isolates of *P. aeruginosa* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

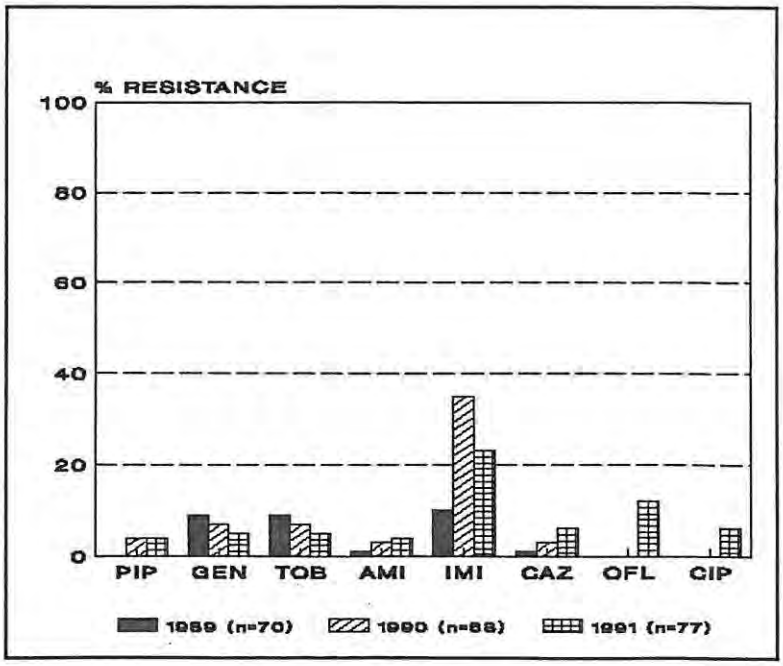

Figure 3.50. Percentage of isolates of *P. aeruginosa* from PHPE (ICU) showing resistance to a range of antibiotics over the three year period 1989-1991.

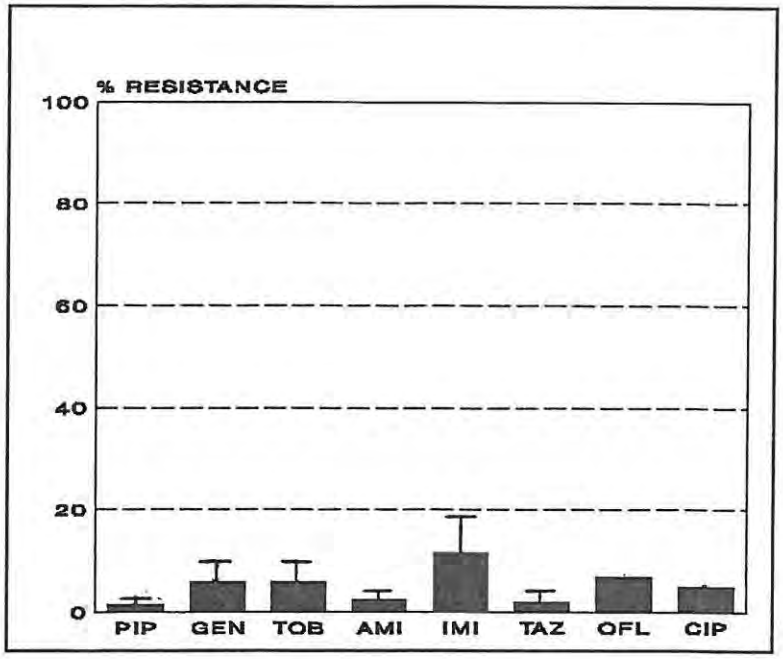

Figure 3.51. The mean of resistant isolates of *P. aeruginosa* for PHPE (whole hospital). Results reported with one standard deviation.

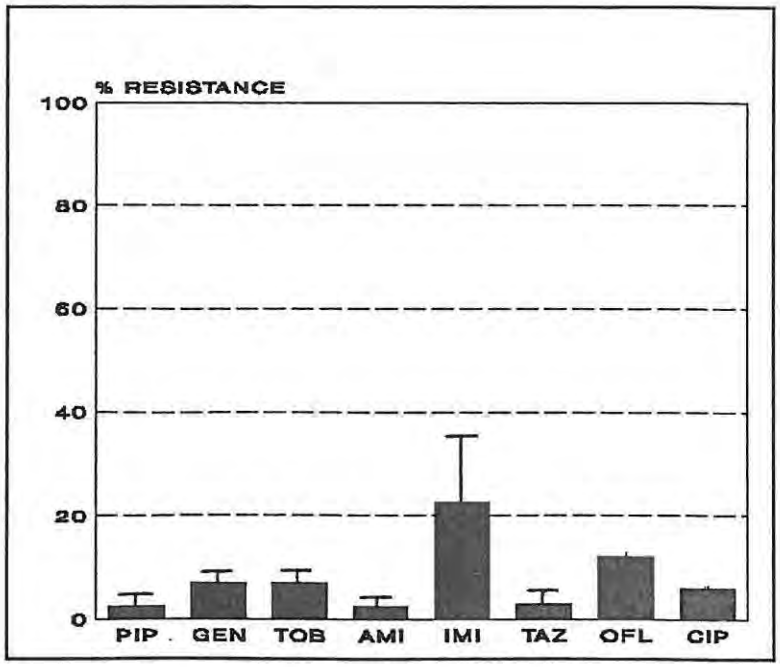

Figure 3.52. The mean of resistant isolates of *P. aeruginosa* for PHPE (ICU). Results reported with one standard deviation.

Table 3.37. Comparison of percentage resistant isolates of *P aeruginosa* between the whole hospital and ICU over the three year period 1989-1991.

	1989		1990		1991	
Antibiotic	**Hosp**	**ICU**	**Hosp**	**ICU**	**Hosp**	**ICU**
PIP	0	0	2	4	3	4
GEN	5	9	10	7	3	5
TOB	5	9	10	7	3	5
AMI	1	1	4	3	3	4
TAZ	1	1	1	3	4	6
IMI	4	10	18	35	13	23
OFL	NT	NT	NT	0*	7	12
CIP	NT	NT	NT	NT	5	6

* = Tested in fourth quarter only.
NT = Not tested

In the comparison between the whole hospital and ICU, the percentage resistance of ICU is higher than that recorded for the whole hospital except for the aminoglycosides which showed a decrease in 1990.

The comparison of the change in resistance patterns over the three year period was made to determine whether any increase or decrease in percent resistance was statistically significant and it was found that resistance of *P. aeruginosa* isolates from the whole hospital to piperacillin and imipenem have shown a statistically significant increase and to gentamicin a statistically significant decrease. In the case of the ICU imipenem, ofloxacin and ciprofloxacin showed an increase in resistance that was statistically significant (Tables 3.38. and 3.39.).

Table 3.38. Test for proportions comparing % resistance of *P. aeruginosa* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
PIP	1,6537	#	0,5421	#	2,1539	*
GEN	1,6295	#	2,3792	**	0,9286	#
TOB	1,6295	#	2,3792	**	0,9286	#
AMI	1,6203	#	0,4562	#	1,2643	#
IMI	3,8539	**	1,1608	#	2,8865	**
TAZ	0	#	1,6517	#	1,6977	#
OFL	NT		3,3601	**	3,3601	**
CIP	NT		2,8098	**	2,8098	**

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

Table 3.39. Test for proportions comparing % resistance of *P. aeruginosa* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
PIP	1,6832	#	0	#	1,7912	#
GEN	0,4336	#	0,5041	#	0,9463	#
TOB	0,4336	#	0,5041	#	0,9463	#
AMI	0,8382	#	0,3285	#	1,1857	#
IMI	3,6736	**	1,5971	#	2,1710	*
TAZ	0,8382	#	0,8807	#	1,6914	#
OFL	NT		3,2404	**	3,2404	**
CIP	NT		2,2170	*	2,2170	*

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

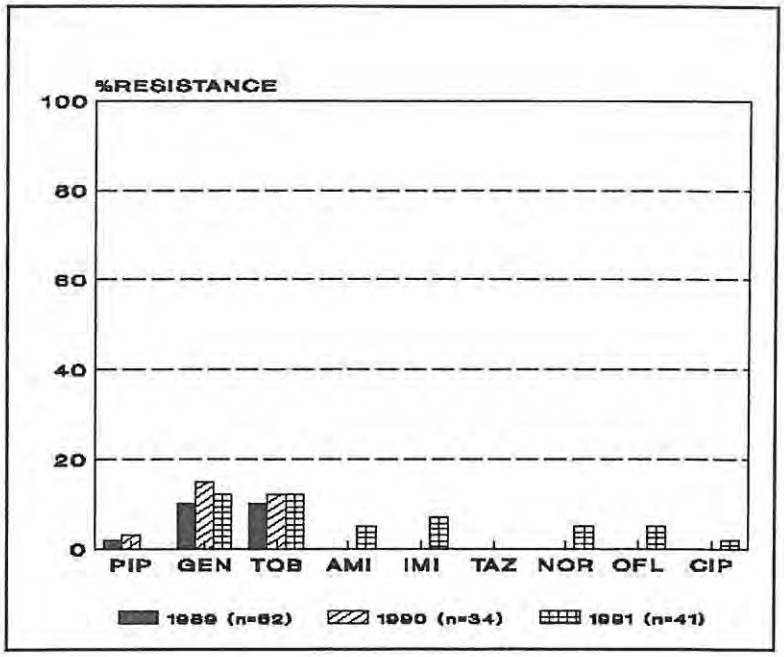

Figure 3.53. Percentage of isolates from urine specimens of *P. aeruginosa* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

3.2.6.1. *PSEUDOMONAS AERUGINOSA* ISOLATES FROM URINE SPECIMENS

Figures 3.53. presents results of annual resistance patterns for the whole hospital for the study period, 1989 to 1991. The number of isolates recorded from the whole hospital for 1989, 1990 and 1991, were 62, 34 and 41 respectively. The number of isolates recorded from OPD were 9 in 1990 and 5 in 1991, with nil percent resistance. The percent resistance to all the antibiotics tested were 15% or below and no increase or decrease in resistance proved to be statistically significant. (Table 3.40.) No resistance was recorded to ceftazidime.

Table 3.40. Test for proportions comparing % resistance of *P. aeruginosa* (urine) isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
PIP	0,2921	#	1,0254	#	1,1249	#
GEN	0,6933	#	0,3772	#	0,3152	#
TOB	0,2963	#	0	#	0,3152	#
AMI	0	#	1,4690	#	1,4690	#
NOR	NT		1,4690	#	NT	
IMI	NT		1,7567	#	NT	
TAZ	NT		0	#	NT	
OFL	NT		1,4690	#	NT	
CIP	NT		0,9147	#	NT	

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.7. *SERRATIA MARCESCENS*

The percentage of resistant isolates of *S. marcescens* from PHPE to a range of antibiotics is presented for the three year study period 1989 to 1991.

Figure 3.54. presents results of annual resistance patterns for the whole hospital. In 1989, 1990 and 1991, 36, 17 and 24 isolates of *S. marcescens* respectively were recorded. Figure 3.55. reports the mean of percentage resistance for isolates from PHPE and Table 3.41. presents a statistical evaluation of changing patterns of resistance for the hospital.

The results showed a pattern of increasing resistance to tetracycline and a decreasing resistance to cefoxitin. These trends over the three year period were found to be statistically significant changes (Table 3.41.).

The numbers of isolates of *S. marcescens* recorded were too low in the ICU to report a comparison between the whole hospital and ICU.

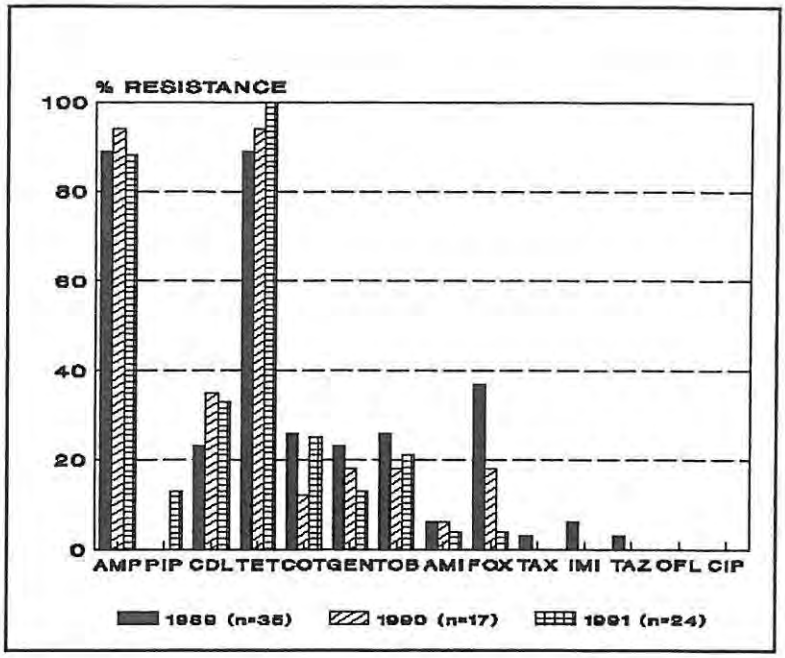

Figure 3.54. Percentage of isolates of *S. marcescens* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

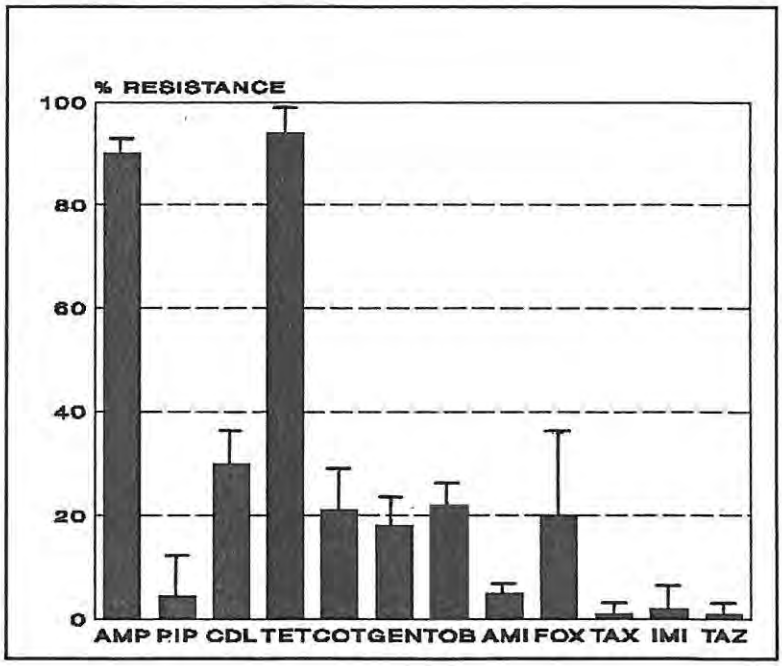

Figure 3.55. The mean of resistant isolates of *S. marcescens* for PHPE (whole hospital). Results reported with one standard deviation.

Table 3.41. Test for proportions comparing % resistance of *S. marcescens* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
AMP	0,6394	#	0,6830	#	0,1179	#
PIP	0	#	1,8937	#	1,8937	#
CDL	0,8836	#	0,1331	#	0,8370	#
TET	0,6394	#	1,0417	#	2,0799	*
COT	1,2938	#	1,0978	#	0,0867	#
GEN	0,4265	#	0,4320	#	1,0116	#
TOB	0,6718	#	0,2402	#	0,4488	#
AMI	0	#	0,2852	#	0,3529	#
FOX	1,5340	#	1,3806	#	3,6300	**
TAX	1,0404	#	0	#	1,0404	#
IMI	1,4947	#	0	#	1,4947	#
TAZ	1,0404	#	0	#	1,0404	#
OFL	NT		0	#	0	#
CIP	NT		0	#	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

3.2.8. *XANTHOMONAS MALTOPHILIA*

The percentage of resistant isolates of *X. maltophilia* from PHPE to a range of eight antibiotics is presented for the study period 1989 to 1991.

Figure 3.56. presents results of annual resistance patterns for the whole hospital. In 1989, 1990 and 1991, 13, 12 and 16 isolates respectively, of *X. maltophilia* were recorded. Figure 3.57. reports the mean of percentage resistance for isolates from PHPE and Table 3.42. presents a statistical evaluation of changing resistance patterns for the hospital.

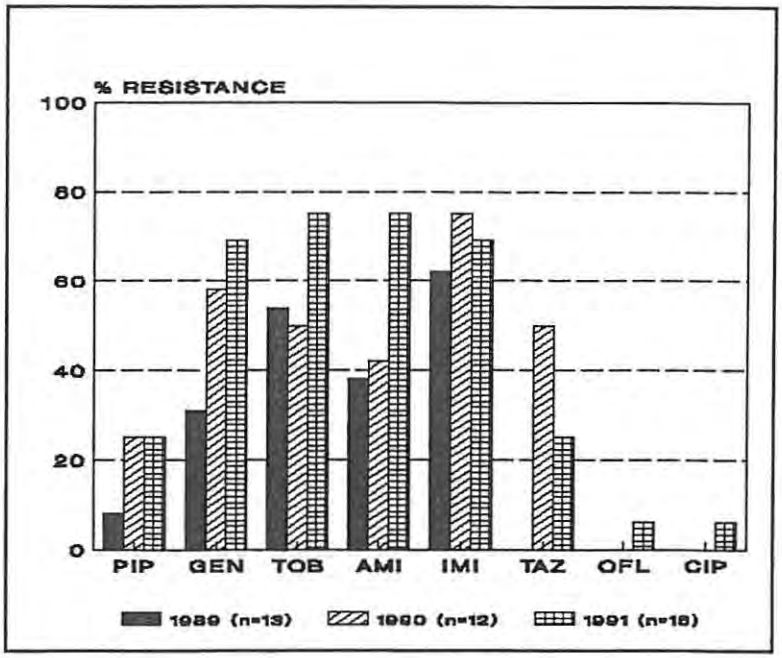

Figure 3.56. Percentage of isolates of *X. maltophilia* from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

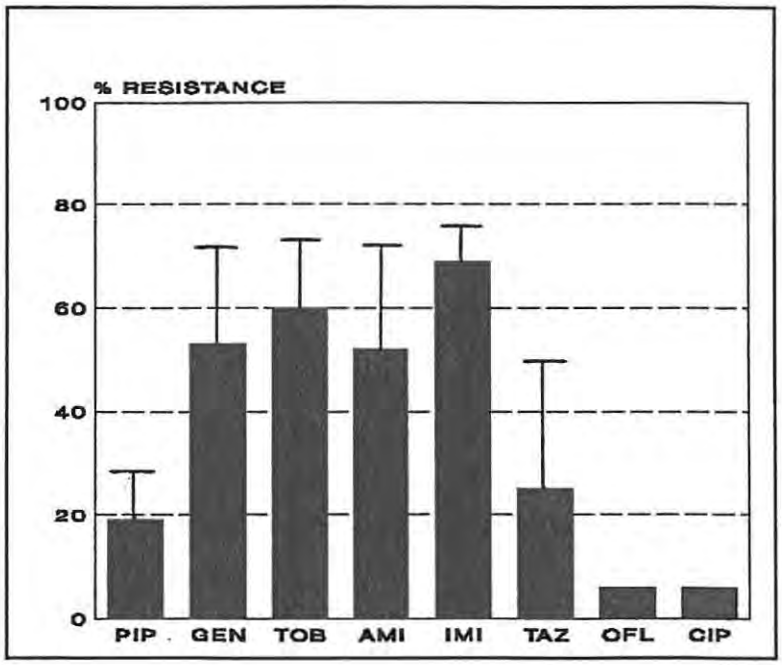

Figure 3.57. The mean of resistant isolates of *X. maltophilia* for PHPE (whole hospital). Results reported with one standard deviation.

Table 3.42. Test for proportions comparing % resistance of *X. maltophilia* isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	1989/1990		1990/1991		1989/1991	
PIP	1,1652	#	0	#	1,2895	#
GEN	1,4084	#	0,5995	#	2,2004	*
TOB	0,2001	#	1,3856	#	1,1961	#
AMI	0,2041	#	1,8442	#	2,1419	*
IMI	0,7077	#	0,3524	#	0,3944	#
TAZ	3,4641	**	1,3856	#	2,3094	*

Started testing TAZ in 4th quarter 1989.

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance
NT = not tested

The results showed a trend of increasing resistance to piperacillin, gentamicin, tobramycin, amikacin and imipenem. Only in the case of piperacillin, ofloxacin and ciprofloxacin was the resistance below 20% of isolates.

The comparison of the change in resistance patterns over the three year period was made to determine whether any increase or decrease in percent resistance was statistically significant and it was found that resistance of *X. maltophilia* isolates to gentamicin and amikacin has shown a statistically significant increase and to ceftazidime a statistically significant decrease, 1990 to 1991. Ciprofloxacin and ofloxacin, tested against this organism in 1991, were recorded as 6 percent resistance for both for the whole hospital. The numbers of isolates of *X. maltophilia* recorded were too low in the ICU to report a comparison between the whole hospital and ICU.

Table 3.43. Comparison of percent resistant and intermediate strains of Gram-negative bacilli to newer agents.

		1989		1990		1991	
Organism	**Antibiotic**	**R**	**I**	**R**	**I**	**R**	**I**
A. anitratus	TAZ	0	2	31	34	39	22
	IMI	10	30	7	9	12	6
	OFL	-	-	0	0	2	22
	CIP	-	-	-	-	0	22
E. cloacae	TAZ	0	2	12	0	22	2
	IMI	8	11	2	20	3	9
	OFL	-	-	0	0	0	5
	CIP	-	-	-	-	0	5
E. coli	TAZ	0	1	2	0	0	1
	IMI	0	1	1	1	1	1
	OFL	-	-	0	0	1	1
	CIP	-	-	-	-	0	2
K. aerogenes	TAZ	0	1	0	4	1	4
	IMI	0	6	0	0	0	4
	OFL	-	-	0	0	0	12
	CIP	-	-	-	-	0	7
P. mirabilis	TAZ	0	0	0	1	0	0
	IMI	2	2	1	4	2	5
	OFL	-	-	0	0	0	6
	CIP	-	-	-	-	0	1
S. marcescens	TAZ	3	0	0	0	0	0
	IMI	6	6	0	0	0	0
	OFL	-	-	0	0	0	0
	CIP	-	-	-	-	0	4
P. aeruginosa	TAZ	1	0	1	2	4	5
	IMI	4	3	18	3	13	3
	OFL	-	-	0	0	7	3
	CIP	-	-	-	-	5	2
X. maltophilia	TAZ	0	0	50	8	25	31
	IMI	62	6	75	0	69	0
	OFL	-	-	0	0	6	31
	CIP	-	-	-	-	6	25

- = not tested R = Resistant I = Intermediate

Table 3.43. presents a comparison of the percentage resistance and intermediate susceptibility to the newer agents tested against the Gram-negative bacilli. Ofloxacin and ciprofloxacin show intermediate susceptibility to most of the organisms.

3.2.9. COLIFORM ISOLATES FROM URINE SPECIMENS

This group of organisms consists of a variety of Gram negative bacilli excluding Pseudomonas species. They are not fully identified for reasons of cost and turn-around-time, and include *E. coli*, Klebsiella species, Enterobacter species and Proteus species amongst others.

Figures 3.58. and 3.59. present results of annual resistance patterns for the whole hospital for the period 1989 to 1991 and for OPD for 1990 and 1991. In 1989, 1990 and 1991, 91, 55 and 127 Coliform isolates were recorded from the whole hospital and in 1990 and 1991, 42 and 46 from OPD respectively. Over 60% of isolates showed resistance to ampicillin and cotrimoxazole and over 80% to sulphonamides in both the whole hospital and OPD. No resistance was found to nicene in OPD and nalidixic acid showed a percent resistance of below 20%.

Table 3.44. reports a comparison of percentage resistance between the whole hospital and OPD. In 1990, OPD resistance figures were higher than the whole hospital except for nitrofurantoin. Whereas in 1991, the whole hospital resistance figures were higher than OPD except for sulphonamides which were similar.

Tables 3.45. and 3.46. presents a statistical evaluation of changing patterns of resistance for the whole hospital and OPD respectively. It was found that resistance of Coliform isolates from the whole hospital to nitrofurantoin has shown a statistically significant increase and to nicene a significant decrease.

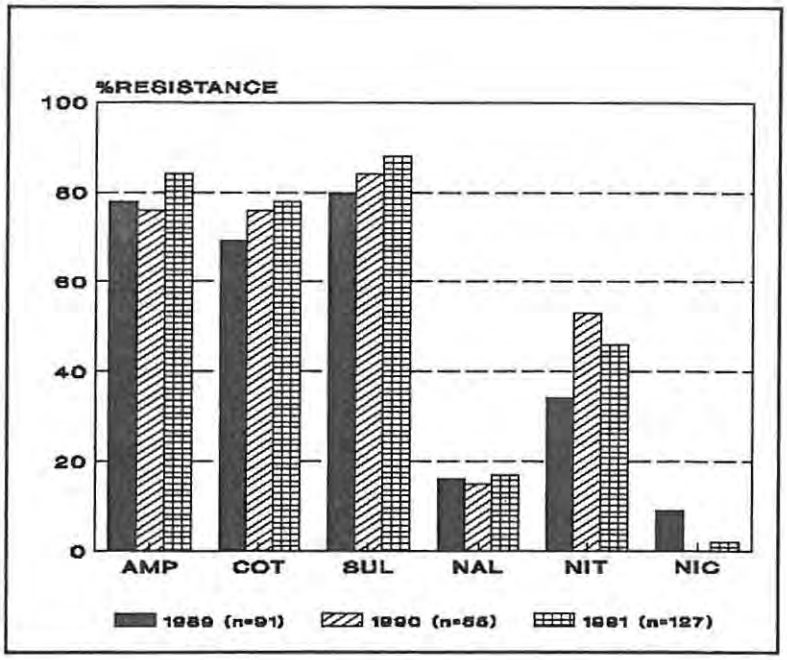

Figure 3.58. Percentage of isolates from urine specimens of Coliforms from PHPE (whole hospital) showing resistance to a range of antibiotics over the three year period 1989-1991.

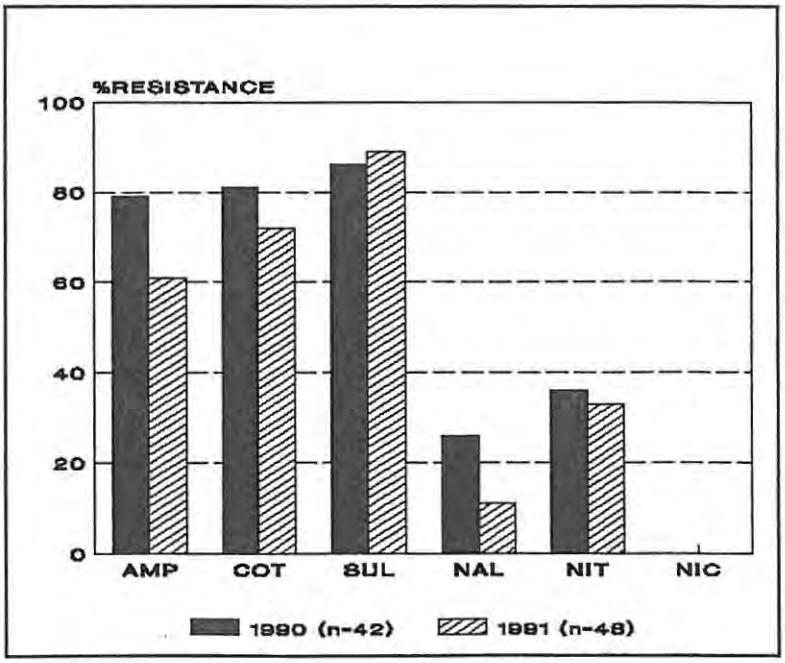

Figure 3.59. Percentage of isolates from urine specimens of Coliforms from PHPE (OPD) showing resistance to a range of antibiotics over the two year period 1990-1991.

Table 3.44. Comparison of percentage resistant isolates of Coliforms between the whole hospital and OPD over the three year period 1989-1991.

	1989	1990		1991	
Antibiotic	**Hosp**	**Hosp**	**OPD**	**Hosp**	**OPD**
AMP	78	76	79	84	61
COT	69	76	81	78	72
SUL	80	84	86	88	89
NAL	16	15	26	17	11
NIT	34	53	36	46	33
NIC	9	0	0	2	0

Table 3.45. Test for proportions comparing % resistance of Coliforms (urine) isolates in PHPE (whole hospital) over the periods 1989/1990, 1990/1991 and 1989/1991.

Antibiotic	**1989/1990**		**1990/1991**		**1989/1991**	
AMP	0,2773	#	1,2095	#	1,1058	#
COT	0,9299	#	0,2927	#	1,4792	#
SUL	0,6171	#	0,6989	#	1,5720	#
NAC	0,1623	#	0,3415	#	0,1966	#
NIT	2,2717	*	0,8692	#	1,8046	#
NIC	3,000	**	1,6099	#	2,1558	*

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

Table 3.46. Test for proportions comparing % resistance of Coliform (urine) isolates in PHPE (OPD) over the period, 1990/1991.

Antibiotic	**1990/1991**	
AMP	1,8847	#
COT	1,0033	#
SUL	0,4245	#
NAL	1,8313	#
NIT	0,2957	#
NIC	0	#

* = 5% level of significance
** = 1% level of significance
\# = above 5% level of significance

3.2.10. PATTERNS OF CHANGING RESISTANCE

Increased resistance to certain antibiotics was found to occur in a number of organisms and certain organisms show changing patterns of resistance to a variety of antibiotics.

Table 3.47. summarises the evaluation of the statistically significant changes observed and was used to determine which antibiotics should be investigated more fully and which organisms would be of interest for comparing with OPD. It was decided that cotrimoxazole, amikacin, ampicillin, ceftazidime and piperacillin would be plotted against the organisms. The comparison with OPD isolates was not made as the numbers of isolates were too low for a statistically significant evaluation.

It is evident that a number of organisms are showing increasing patterns of resistance to more than one antibiotic and in the case of *E. cloacae*, this multiple resistance is to four antibiotics. However, a decrease in resistance is also observed and in Klebsiella aerogenes, the significant changes are a decrease in resistance to four antibiotics. A second feature that emerges from the evaluation of changing resistance patterns over the period, is that resistance to a particular antibiotic is emerging simultaneously in more than one organism with cotrimoxazole and amikacin showing this pattern.

Table 3.47. Summary of change in resistance patterns showing statistically significant differences over the three year period.

	AMP	PIP	CDL	TET	COT	GEN	TOB	AMI	FOX	TAX	TAZ	IMI	Total increase of resistance of organisms	Total decrease of resistance of organisms
A. anitratus	- *							+ *			+ **		2	1
E. cloacae		+ **			+ **					+ **	+ **		4	0
K. aerogenes	- **	- **				- **	- **						0	4
P. mirabilis													0	0
E. coli			- *		+ *								1	1
S. marcescens				+ *									1	0
P. aeruginosa												+ **	1	0
X. maltophilia						+ *		+ *			- *		2	1
Total increase of resistance of antibiotic	0	1	0	1	2	1	0	2	0	1	2	1		
Total decrease of resistance of antibiotic	2	1	1	0	0	1	1	0	0	0	1	0		

* = 5% level of significance
** = 1% level of significance
\+ = increase in resistance
\- = decrease in resistance

3.2.10.1. COMMON RESISTANCE PATTERNS

Figures 3.60. - 3.69. represent the resistance pattern in a range of organisms to the following antibiotics:

Cotrimoxazole
Amikacin
Ampicillin
Ceftazidime
Piperacillin

E. cloacae and *E. coli* show a statistically significant increase in resistance to cotrimoxazole 1989 to 1991, as presented in Figure 3.60. Over 60% of *A. anitratus*, *K. aerogenes* and *E. coli* are resistant to this antibiotic with *P. mirabilis* isolates showing a mean resistance of 40% (Figure 3.61; Tables 3.20. and 3.23.).

X. maltophilia is the most resistant of the eight organisms to amikacin with a mean of 52%. *A. anitratus* isolates show a mean resistance of 22%. The increases in percent resistance 1989 to 1991, are statistically significant for these two organisms (Figures 3.62. and 3.63., Tables 3.42. and 3.17.).

Ampicillin resistance was over 80% to all organisms reported except for *E. coli* and *P. mirabilis* which showed mean percentages of 75% and 45%, respectively (Figures 3.64. and 3.65.). The decreases in percent resistance against *A. anitratus* and *K. aerogenes* are statistically significant (Tables 3.17. and 3.29.).

The increases in percentage resistance to ceftazidime in *A. anitratus*, *E. cloacae* and *X. maltophilia* isolates 1989 to 1991, are statistically significant with their mean percentage resistance as 35%, 17% and 25%, respectively (Figures 3.66. and 3.67., Tables 3.20. and 3.42.). The other organisms show 5% and less, resistance to the antibiotic.

Three peaks of mean resistance to piperacillin are evident in Figures 3.68. and 3.69., these being *A. anitratus*, *K. aerogenes* and *X. maltophilia*. Statistically significant changes occurred as an increase in *E. cloacae* and a decrease in *K. aerogenes*, 1989 to 1991 (Tables 3.20. and 3.29.). The other six organisms showed 15% or less mean resistance to this antibiotic.

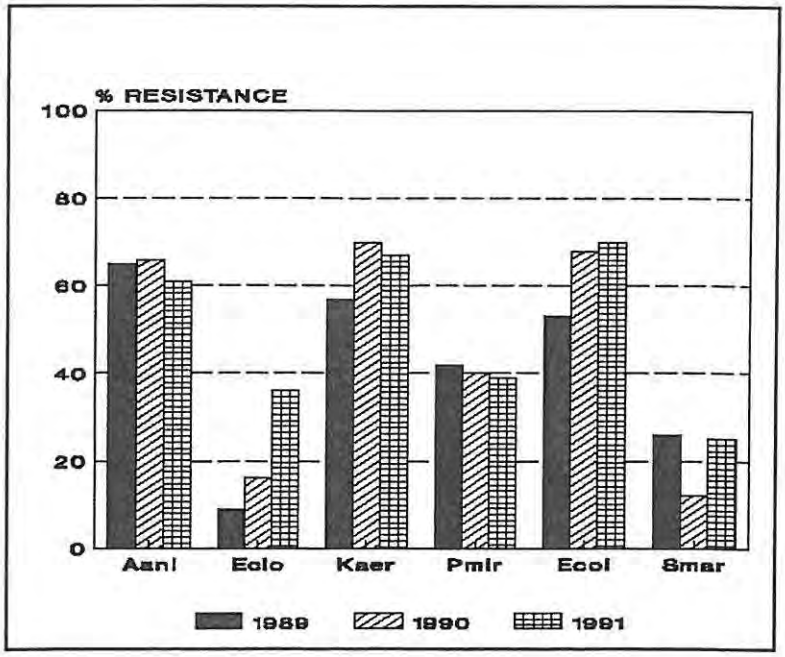

Figure 3.60. Percentage resistance to cotrimoxazole for PHPE (whole hospital) of six organisms over the three year period 1989-1991.

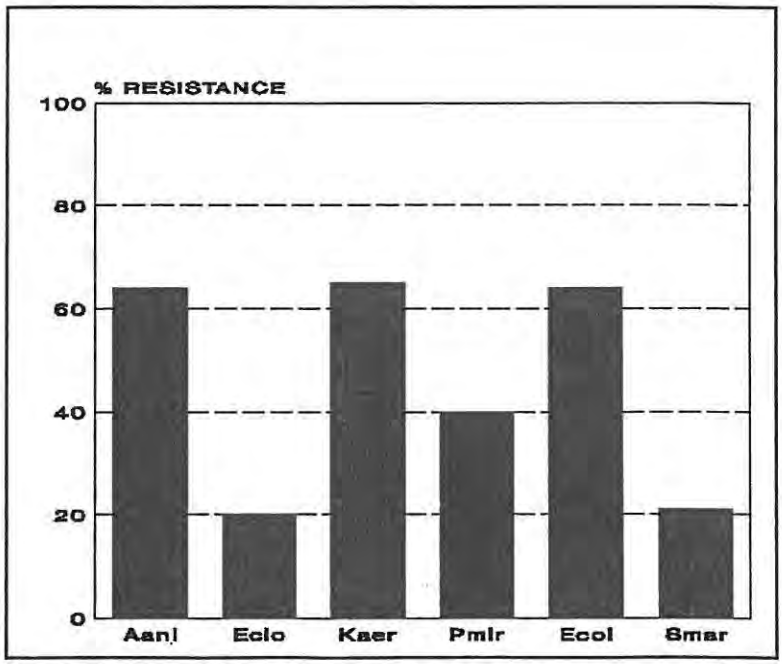

Figure 3.61. The mean of resistance to cotrimoxazole for PHPE (whole hospital) of six organisms over the three year period 1989-1991.

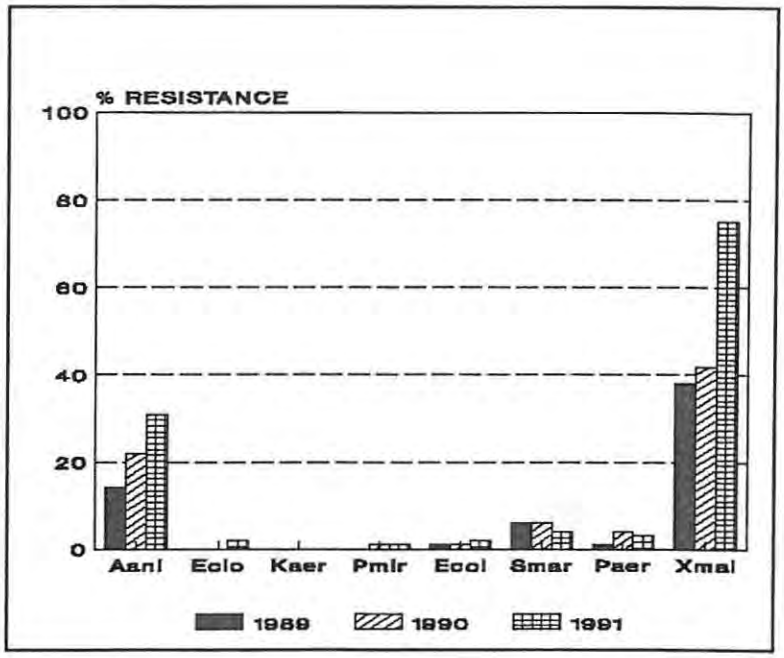

Figure 3.62. Percentage resistance to amikacin for PHPE (whole hospital) of eight organisms over the three year period 1989-1991.

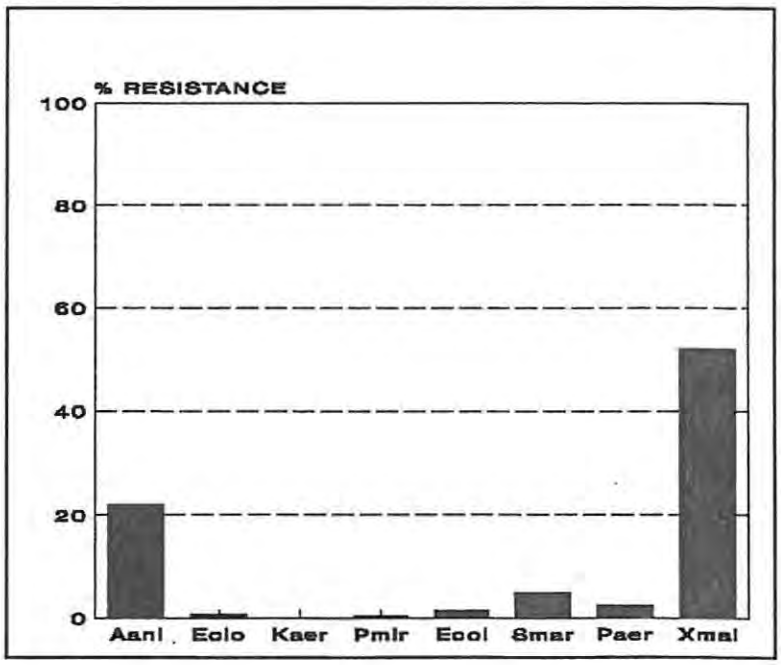

Figure 3.63. The mean of resistance of amikacin for PHPE (whole hospital) of eight organisms over the three year period 1989-1991.

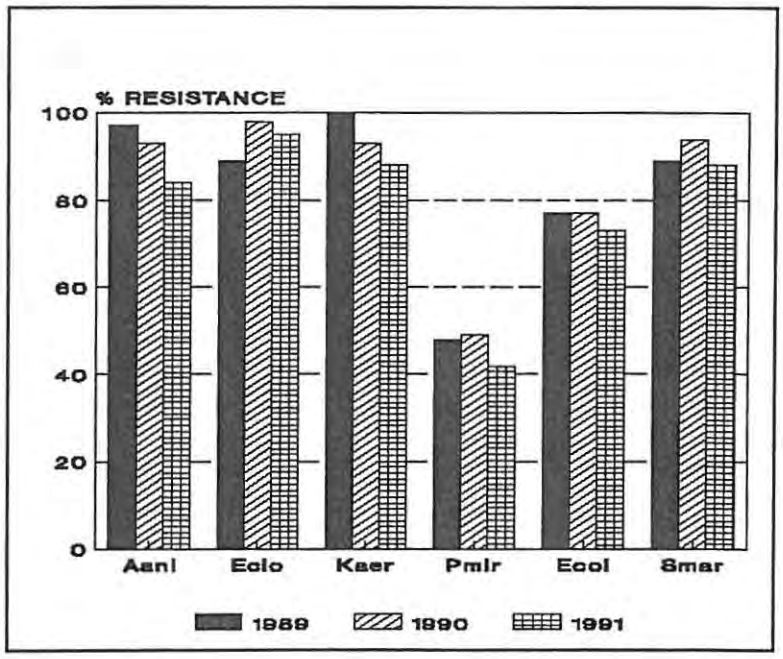

Figure 3.64. Percentage resistance to ampicillin for PHPE (whole hospital) of six organims over the three year period 1989-1991.

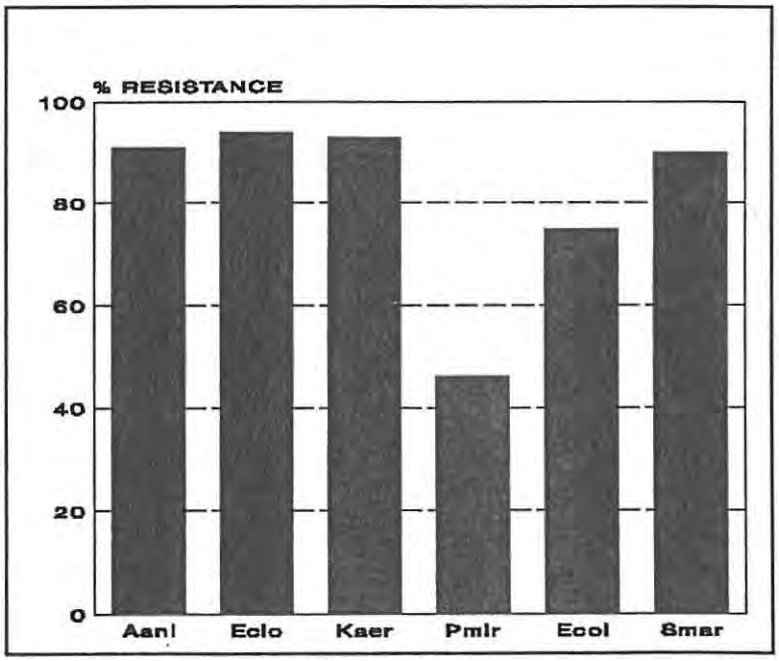

Figure 3.65. The mean of resistance to ampicillin for PHPE (whole hospital of six organisms over the three year period 1989-1991.

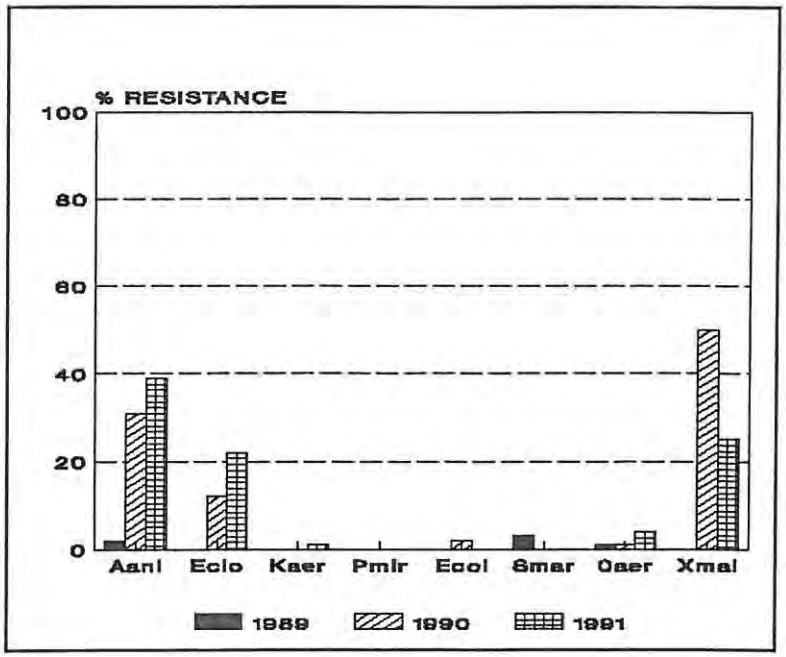

Figure 3.66. Percentage resistance to ceftazidime for PHPE (whole hospital) of eight organisms over the three year period 1989-1991.

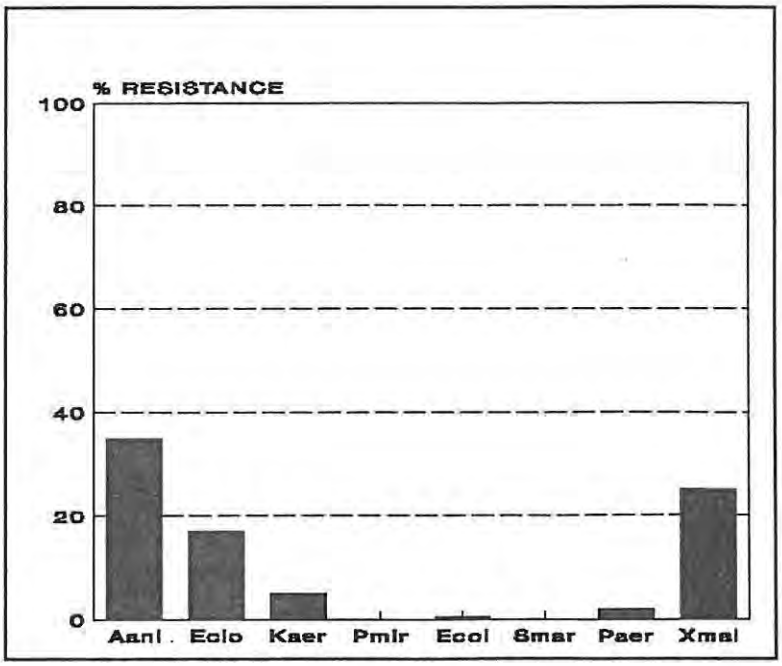

Figure 3.67. The mean of resistance to ceftazidime for PHPE (whole hospital) of eight organisms over the three year period 1989-1991.

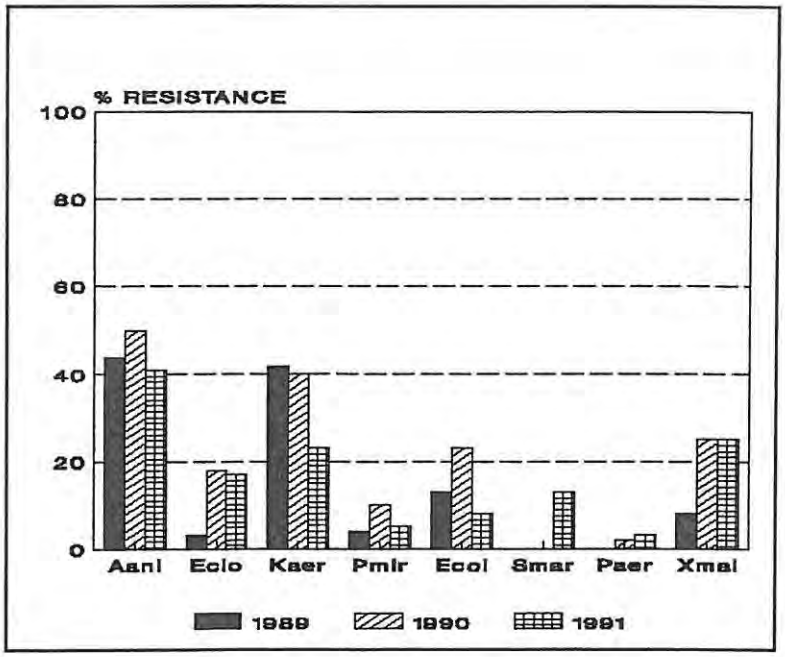

Figure 3.68. Percentage resistance to piperacillin for PHPE (whole hospital) of eight organisms over the three year period 1989-1991.

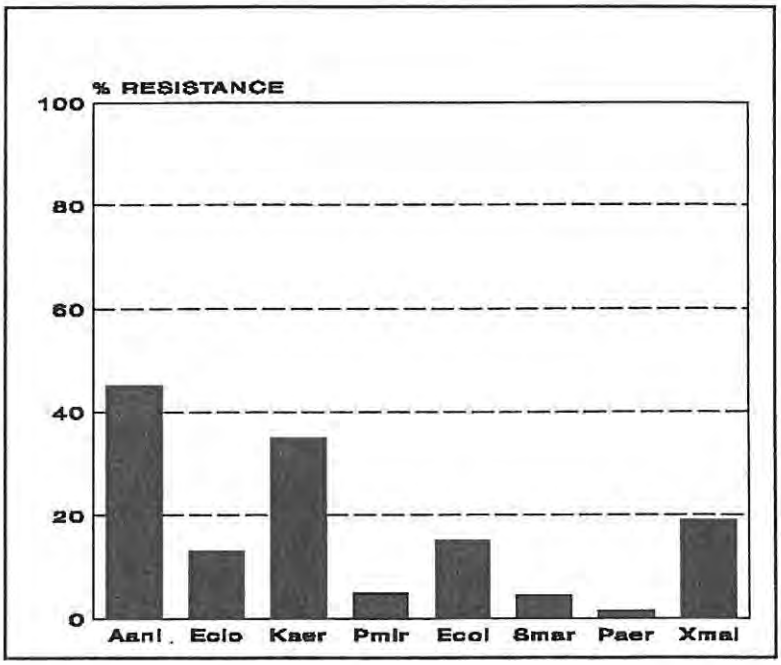

Figure 3.69. The mean of resistance to piperacillin for PHPE (whole hospital) of eight organisms over the three year period 1989-1991.

3.2.11. A COMPARATIVE SUMMARY OF ANTIBIOTIC RESISTANCE

Antibiotic surveillance reports supplied by Bristol-Myers Squibb (Pty) Limited were collated from four hospitals in South Africa: Universitas Hospital, Bloemfontein; Hillbrow Hospital, Johannesburg; Groote Schuur Hospital and Red Cross Childrens' Hospital, Cape Town.

The data from Universitas and Hillbrow Hospitals was for the whole year (1991) while the data from Groote Schuur and Red Cross Hospitals was for nine months of 1991. The program is in the development phase and not all data was being picked up resulting in inaccuracies. However, this is the only source of this type of information and permission to use it was granted by the Chairman of the Antibiotic Study Group of South Africa, Professor P Botha.

Table 3.48. to 3.55. present a comparative summary of percentage resistance between PHPE and the aforementioned hospitals for eight organisms previously described. In Table 3.51. the other hospitals in South Africa call this organism Klebsiella pneumoniae. In the data from Red Cross Childrens' Hospital and to a lesser extent the others, certain antibiotics are not reported on. Universitas Hospital's data appeared to include urine isolates and the numbers of isolates from the Cape Town hospitals were few. However, it was decided to include all data collated as this was all that was available for comparison.

Table 3.48. Comparison of percentage resistance of *A. anitratus* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	Hillbrow	GSH	Red X	P.E.
AMP	81	99	98	96	84
PIP	32	81	33	-	41
CDL	100	-	98	-	90
TET	70	96	-	-	73
COT	47	-	39	26	61
GEN	33	83	79	13	61
TOB	-	48	75	-	63
AMI	28	74	5	0	31
FOX	100	-	92	-	78
TAX	48	78	88	-	49
TAZ	39	62	37	-	39
IMI	12	3,5	16	-	12
CIP	10	2	14	-	0
OFL	0	-	30		2

- = not reported

Table 3.49. Comparison of percentage resistance of *E. cloacae* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	GSH	Red X	P.E.
AMP	93	89	50	95
PIP	40	33	-	17
CDL	34	35	-	23
TET	58	-	-	41
COT	39	9	47	36
GEN	17,7	3	16	3
TOB	3,7	3	-	3
AMI	0,4	0	0	2
FOX	79	74	-	92
TAX	32	-	-	22
TAZ	32	29	-	22
IMI	0	-	-	3
CIP	1	0	-	0
OFL	0	0	-	0

- = not reported

Table 3.50. Comparison of percentage resistance of *E. coli* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	Hillbrow	GSH	Red X	P.E.
AMP	72	65	57	73	73
PIP	22	31	23	-	8
CDL	7	-	14	-	1
TET	65	66	72	-	58
COT	59	-	50	63	73
GEN	2	2,5	3	2,5	1
TOB	2	1,5	3	-	2
AMI	15	1	1	0,5	2
FOX	11	-	0.5	-	4
TAX	2	1	1	-	1
TAZ	5	1	5	-	0
IMI	0,5	0	-	-	1
CIP	0	0.5	1	-	0
OFL	0	-	1	-	1

- = not reported

Table 3.51. Comparison of percentage resistance of *K. aerogenes* isolates in PHPE and *K. pneumoniae* in other S.A. hospitals in 1991.

Antibiotic	Universitas	Hillbrow	GSH	Red X	P.E.
AMP	94	97	97	98	88
PIP	28	21	-	-	23
CDL	33	-	26	-	10
TET	40	50	-	-	49
COT	48	-	28	53	67
GEN	9	13	16	35	16
TOB	7	17	13	-	16
AMI	1	4	0,5	1	0
FOX	7	-	3	-	4
TAX	12	9	20	-	0
TAZ	8	10	50	25 (4 isolates)	1
IMI	0	0	0 (4 isolates)		0
CIP	0,5	2	1	-	0
OFL	0,5	-	4	-	0

- = not reported

Table 3.52. Comparison of percentage resistance of *P. mirabilis* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	Hillbrow	GSH	Red X	P.E.
AMP	42	24	29	50	42
PIP	3	2	- (3 isolates)	-	5
CDL	0 (25 isolates)	-	10	-	3
TET	97	98	100	-	100
COT	29	-	21	38	39
GEN	2	2	5	7	6
TOB	1	1	1	-	3
AMI	0.5	0.5	0	0	1
FOX	0	-	5	-	1
TAX	1	0.5	0	-	0
TAZ	0	0.5	0	-	0
IMI	2	0	0	-	2
CIP	0	0	0	-	0
OFL	0	-	0	-	0

- = not reported

Table 3.53. Comparison of percentage resistance of *S. marcescens* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	Hillbrow	GSH	Red X	P.E.
AMP	97	97	91 (11 isolates)	100	88
PIP	2	11	-	-	13
CDL	29	-	67 (3 isolates)	-	33
TET	96	97	-	-	100
COT	24	-	27 (11 isolates)	38	25
GEN	8	16	27 (11 isolates)	29	13
TOB	11	16	-	-	21
AMI	0	11	0	7	4
FOX	7	-	0	-	4
TAX	2	3	-	-	0
TAZ	0	0	-	-	0
IMI	5	0	-	-	0
CIP	0	0	0	-	0
OFL	0	-	-	-	0

- = not reported

Table 3.54. Comparison of percentage resistance of *P. aeruginosa* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	Hillbrow	GSH	Red X	P.E.
PIP	3,5	7	1,5	-	3
GEN	25	20	20	11,5	3
TOB	7	18	20	5,5	3
AMI	1,5	6	0,5	3	3
TAZ	8	8	1,5	3	4
IMI	12,5	14	-	17	13
CIP	0,7	2	8,5	0	5
OFL	9	-	14,5	1	7

- = not reported

Table 3.55. Comparison of percentage resistance of *X. maltophilia* isolates in PHPE and other S.A. hospitals in 1991.

Antibiotic	Universitas	Red X	P.E.
PIP	34	-	25
COT	39	67	-
GEN	80	30	69
TOB	74	32	75
AMI	70	30	75
TAZ	27	11	25
IMI	100	100	69
CIP	4	5	6
OFL	0	-	6

- = not reported

3.3. ANTIBIOTIC USAGE

A variety of twenty-four antibiotics were used in the hospital over the period 1989 - 1991. Information from the pharmacy was obtained as to the usage of these agents and the conversion factors for converting into dosage figures. Not all the dosage information was available because of package differences and the different forms of availability of some agents eg. tablets, suspensions, ampules etc.

Ward stock sheets were checked but this was found to be very inaccurate according to ward and pharmacy staff, therefore gross monthly figures from pharmacy stock sheets were used. Only figures for nine months of 1990 were available and have been extrapolated for twelve months. Bearing the above facts in mind Table 3.56. presents a list of agents that were able to be converted into doses and their relevant doses for 1990 and 1991. Analysis of the figures show that the drug usage pattern did not change significantly. Unfortunately there was not adequate data to correlate changing patterns of antibiotic usage with resistance changes, one of the most important aspects of this study.

Ampicillin, penicillin, fucidin, tetracycline, erythromycin, clindamycin, vancomycin, nicene, nitrofuratoin and nalidixic acid were all included in the investigation. However, they were not all able to be converted into dose related figures as they are prepacked or tablets and suspensions. The comment made by the Chief Pharmacist was that the hospital uses a lot of second generation cephalosporins and aminoglycosides (Table 3.56.).

Table 3.56. Number of doses per antibiotic over the period 1990 and 1991.

Antibiotic	1990	1991
Piperacillin	2600	2055
Cefamandole	9467	10085
Cotrimoxazole	433	255
Gentamicin	4967	4756
Tobramycin	4627	5850
Netilmicin	2100	2270
Amikacin	2947	2725
Cefoxitin	27467	28000
Cefotaxime	1120	1340
Imipenem	300	780
Ceftazidime	950	854
Ciprofloxacin	0	980
Ofloxacin	0	130

Table 3.57. Time-table of the introduction of newer agents tested for in the laboratory and first used in the hospital.

Agent	Laboratory	Hospital
TAZ	27/10/89 (all Pseudomonas species Sept 1990)	Sept 1990
IMI	27/10/89 ICU only	Sept 1990
CIP	1991 ICU only	1991
OFL	Oct 1990 ICU only	1991

Table 3.57. reports the dates of introduction of the newer agents into the hospital and when testing started in the laboratory. The agents for ICU only were tested and reported on isolates from the rest of the hospital if the organism showed resistance to most or all of the routine antibiotics.

CHAPTER 4

4. DISCUSSION

Infections caused by resistant bacteria have been a fact of life ever since effective antibacterial drugs became available. While the percentage resistance of the clinical isolates evaluated in this study generally follows the trends observed in other centres in South Africa and other countries, there were some notable differences.

4.1. STAPHYLOCOCCUS SPECIES

The high incidence of drug resistance in 1989 observed with *S. aureus* and *S. epidermidis* (Figures 3.1., 3.2., 3.9. and 3.10.) are due to the inclusion of methicillin resistant strains in 1989 only. In 1990 and 1991, methicillin sensitive and resistant strains were separated to evaluate and compare the resistance patterns of each. MSSE isolates were considerably more resistant than MSSA particularly to tetracycline, erythromycin, cotrimoxazole, fusidic acid, clindamycin and gentamicin and tobramycin, the differences being statistically significant (Table 3.8.).

With reference to the results presented in Table 3.8., MRSA isolates were found to be less resistant than MRSE stains except against the drugs tetracycline, erythromycin and gentamicin. Resistance to fusidic acid, clindamycin and imipenem was found to be significantly higher for MRSE isolates.

The methicillin resistant strains of *S. aureus* and *S. epidermidis* increased from 1989 to 1990 and then remained static for 1991; 22% and 43% in 1989 and 29% and 47% in 1990 and 1991 respectively (Table 3.9.). In a Nigerian hospital methicillin resistance to *S. aureus* was not found (Olusanya *et al.*, 1991), while in the N.N.I.S. report of 1984 resistance to methicillin was 14% and 56%, respectively (Isenberg, 1988).

There was a statistically significant decrease in percent resistance to cefamandole by both MSSA and MSSE isolates; this is not related to the agent's usage as this in fact increased slightly over the period as shown in Table 3.56. Resistance to vancomycin was not detected over the study period.

The percent resistance of *S. aureus* isolates in this study for 1989 was higher or in the case of clindamycin equal to that given for 1987 in Durban and in the N.N.I.S. report of 1984 (van den Ende, 1989; Isenberg, 1988). Findings in this study were: penicillin 89%; cefamandole 23%; tetracycline 26%; erythromycin 21%; cotrimoxazole 18%; fusidic acid 2%; clindamycin 11%; gentamicin 19% and methicillin 22% (Figure 3.1. and Table 3.9.).

The findings of this study concur with other workers that *S. epidermidis* is overall more resistant to antibiotics than *S. aureus* (Davies *et al.*, 1986; Eykyn, 1988; McGowan, 1988; van den Ende, 1989).

A comparison of percent resistant and intermediate strains of staphylococci to newer agents i.e., imipenem, ofloxacin and ciprofloxacin (Table 3.10.) shows that while in some instances the increase in resistance is minimal, there is a decrease in susceptibility to all of these agents when the intermediate results are compared for 1990 and 1991 from the whole hospital.

In comparison with the findings of Daum *et al.*, (1990) this study found an emergence of resistance to ciprofloxacin among MRSA but no resistance among *S. aureus* isolates.

4.2. ENTEROCOCCUS SPECIES

Our findings of a mean of 4 and 20 percent ampicillin resistance in *E. faecalis* and *E. faecium* isolates respectively is similar to the trends reported in the United Kingdom and the N.N.I.S. report (Gray *et al.*, 1991; Isenberg, 1988).

The increase of resistance to penicillin in both enterococcal species is statistically significant and ampicillin and piperacillin would appear to be agents of choice particularly in the case of *E. faecalis*.

4.3. *ACINETOBACTER ANITRATUS*

A. anitratus proved to be the most resistant Gram-negative bacillus of this study showing a high percentage of resistance to ten of the fourteen agents reported. The quinolones, imipenem and amikacin appear to be the best choice of agent for treatment, in order of increasing resistance respectively. The mean gentamicin resistance of 63% for the whole hospital and of 73% for the ICU, is much higher than other studies (McGowan *et al.*, 1993; Moaz *et al.*, 1989). Compared to other S.A. hospitals *A. anitratus* in this study has a lower percent resistance than Hillbrow and Groote Schuur Hospitals and higher than Universitas Hospital (Table 3.48.). Monthly trends of statistically significant changes did not demonstrate any useful information or seasonal variance as shown in Figure 3.27.

4.4. *ENTEROBACTER CLOACAE*

The pattern of increasing resistance to cotrimoxazole, cefotaxime and ceftazidime among isolates of *E. cloacae* from the whole hospital, and including piperacillin among isolates from the ICU, is disturbing. John Jr *et al.*, (1982) found that the newer agents e.g. cefazidime were active against *E. cloacae* while in this study in 1991 the percent resistance is over 20 percent to this agent (Table 3.19.). The aminoglycosides and the quinolones prove to be the agents of choice where this organism is implicated in infection. Except for tetracycline and cotrimoxazole *E. cloacae* has lower percent resistance figures than that of the N.N.I.S. report (Isenberg, 1988).

Compared to the other S.A. hospitals, PHPE has lower resistance figures to most agents. The notable exceptions being amikacin and cefoxitin in all instances as shown in Table 3.49.

Monthly trends showed two peaks for cotrimoxazole in May 1990 and 1991, two peaks for piperacillin in July and October 1990 and a peak for ceftazidime in July 1990. However, no meaningful information could be determined from this data (Figure 3.32.).

4.5. *ESCHERICHIA COLI*

E. coli isolates from the PHPE are very susceptible to most agents in use, the exceptions being ampicillin (76%), tetracycline (57%) and cotrimoxazole (64%), with respective percent resistances given in brackets. In Figures 3.33. and 3.34. and Table 3.22. resistance to piperacillin peaked to 23% in 1990 in the whole hospital and 25% in ICU, otherwise the resistance was fairly low. The mean gentamicin resistance for the whole hospital, 3% and the ICU 5%, is higher than other studies i.e. 1,6% in Riyadh (Moaz *et al.*, 1989) and 1% in the N.N.I.S. report (Isenberg, 1988). Compared to the other S.A. hospitals, *E. coli* strains from PHPE are much more resistant to cotrimoxazole (Table 3.50.).

E. coli isolates from urine specimens were found to be highly resistant to ampicillin, cotrimoxazole and sulphonamides. Isolates from the out-patients were slightly less resistant but percent resistance of over 60% was shown. The urinary antimicrobials, nalidixic acid, nitrofurantoin and nicene showed a resistance of 11% and below.

4.6. *KLEBSIELLA AEROGENES*

Amikacin, second and third generation cephalosporins, the quinolones and imipenem have a resistance rate of less than 20% for *K. aerogenes* isolates. Over 50% of the isolates are resistant to ampicillin, tetracycline and cotrimoxazole with resistance of 97%, 51% and 65% respectively. Compared to the other S.A. hospitals, *K. aerogenes* strains from PHPE are more resistant to tetracycline, cotrimoxazole, gentamicin and tobramycin (Table 3.51.). However, resistance to amikacin, and in particular cefotaxime and ceftazidime, is much lower.

4.7. *PROTEUS MIRABILIS*

P. mirabilis isolates from PHPE were found to be susceptible to most agents with the exceptions of ampicillin and cotrimoxazole showing between 40 and 50 percent resistance. The decrease in resistance in the ICU to cotrimoxazole and to a lesser degree to ampicillin (1990-1991) as shown in Figure 3.44. and Table 3.13, is encouraging and needs to be monitored to determine whether this trend will continue. The mean gentamicin resistance for the whole hospital, 7% and the ICU 9% is lower than those reported in other studies i.e. 15% in Riyadh (Moaz *et al.*, 1989) and 1% in the N.N.I.S. report (Isenberg, 1988).

Compared to the other S.A. hospitals, *P. mirabilis* isolates from PHPE were found to be similar or marginally more resistant (Table 3.52.).

P. mirabilis isolates from urine specimens showed over 60% resistance to ampicillin, cotrimoxazole and sulphonamides, and over 90% to nitrofurantoin (Table 3.34., Figure 3.47.). Isolates showed a consistently higher susceptibility to nalidixic acid and nicene over the three year period. In 1991, the OPD isolates showed a higher percentage resistance than the whole hospital to the aforementioned agents. In a survey from patients in a district general hospital and local community in the United Kingdom, McGowan *et al* (1993) reported resistance figures of approximately 20% for *P. mirabilis* isolates to ampicillin and sulphonamides, this being quite low compared to the isolates from PHPE urine isolates.

4.8. *PSEUDOMONAS AERUGINOSA*

The mean percent resistance for *P. aeruginosa* isolates as shown by Figures 3.51. and 3.52. is below 10% except for imipenem (12%, whole hospital and 23%, ICU) for both the whole hospital and ICU. The mean gentamicin resistance (6%) is lower than other studies (Isenberg, 1988; Moaz *et al.*, 1989; Neeling *et al.*, 1987). Compared to other S.A. hospitals, *P. aeruginosa* isolates from PHPE show a lower percent resistance except for ciprofloxacin (5%). In Universitas and Hillbrow hospitals ciprofloxacin resistance is reported to be lower than PHPE, as shown in Table 3.54.

P. aeruginosa isolates from urine specimens showed a slightly higher mean percent resistance to gentamicin and tobramycin than those isolated from non-urinary sites and were very susceptible to the other agents tested.

4.9. *SERRATIA MARCESCENS*

Over 80% of *S. marcescens* isolates showed resistance to ampicillin and tetracycline. The mean gentamicin resistance is similar to that found in Riyadh (Moaz *et al.*, 1989) and higher than that reported in the N.N.I.S. survey (Isenberg, 1988) (Figure 3.55.). Isenberg, (1988) also reported 71% and 14% resistance to cefamandole and piperacillin respectively which are higher than those found in this study; 30% and 4,5% respectively. Compared to other S.A. hospitals, *S. marcescens* isolates were more resistant than Universitas, lower than Red Cross Childrens' Hospital and similar to Hillbrow Hospital except amikacin (11%) which had the highest percentage resistance of all the hospitals (Table 3.53.).

4.10. *XANTHOMONAS MALTOPHILIA*

This study has shown an increase in resistance of *X. maltophilia* isolates to most of the agents and over 50% resistance to the aminoglycosides and imipenem (Figure 3.57.). Ceftazidime showed a decrease, 1990 to 1991, and it will be interesting to see if this trend continues. Compared with other S.A. hospitals percentage resistance to amikacin and the quinolones were found to be higher in this study (Table 3.55.).

4.11. COLIFORMS ISOLATED FROM URINE SPECIMENS

Nicene has shown good activity against coliforms, the only agent below 10 percent resistance for both the whole hospital and OPD. Figures in this study compared to the survey from the United Kingdom (McGowan *et al.*, 1993), shows higher resistance to ampicillin (80%) and nitrofurantoin (50%) (Figures 3.58., 3.59., and Table 3.44.).

4.12. INTENSIVE CARE

The methicillin sensitive staphylococcal isolates from the whole hospital are more resistant than those isolated from the ICU only, especially to cefamandole, tetracycline, cotrimoxazole and fucidin (Tables 3.2. and 3.6.). However, the methicillin resistant isolates from the ICU were more resistant than those isolated from the whole hospital (Tables 3.3. and 3.7.). *E. faecalis* was more resistant in hospital isolates to ampicillin, tetracycline and erythromycin and in the ICU isolates, to penicillin and piperacillin (Table 3.8.).

Amongst the Gram-negative bacilli, *A. anitratus* and *P. aeruginosa* isolates from the ICU are more resistant to all the agents than those from the whole hospital (Tables 3.16. and 3.37.). Imipenem showed double the percent resistance in ICU (22.5%) than the whole hospital (11.5%) to *P. aeruginosa* strains.

Overall the ICU isolates are more resistant to piperacillin, clindamycin, second and third generation cephalosporins, the aminoglycosides, the quinolones and imipenem. The whole hospital isolates are more resistant to ampicillin and tetracycline and there is similarity to cotrimoxazole, erythromycin, fucidin and penicillin between the whole hospital and ICU isolates.

Shah *et al* (1991) reported the susceptibilities of Gram-negative aerobes from Intensive Care Units of ten German hospitals and in comparison to this study, *A. anitratus*, *E. cloacae*, *K. aerogenes*, *P. mirabilis* and *E. coli* isolates from PHPE are more resistant, the exception being to piperacillin which showed higher percent resistance compared to our figures.

P. aeruginosa isolates from PHPE proved to be more sensitive than those from the German hospitals cited by Shah *et al.*, (1991) except for imipenem which showed 17% resistance in the German study compared to 22.5% in this study. In 1990 it was reported from the neonatal ICU at Baragwanath Hospital that 13% of Gram-negative bacilli were resistant to amikacin (Liebowitz & Koornhof, 1990). This study showed a 5,6% resistance to amikacin from the ICU at PHPE.

4.13. ANTIBIOTIC USAGE

The antibiotics which could be evaluated for an increase or decrease in usage, showed an overall increase except for piperacillin, cotrimoxazole, gentamicin, amikacin and ceftazidime. The top three agents according to usage are: 1. cefoxitin; 2. aminoglycosides and 3. cefamandole proving that the general statement made by the Chief Pharmacist was indeed a fact.

Amikacin is the aminoglycoside with the least percent resistance for both the whole hospital and the ICU. Excluding the figures for *X. maltophilia* the following are the percent resistance to the aminoglycosides: amikacin 5%, tobramycin 18% and gentamicin 20%. This is similar to the findings at Tygerberg hospital (Hesseling, 1993).

When an analysis and comparison of resistance patterns was done regarding changes within months and years it was found that the monthly changes were too erratic to be meaningful. However, year by year changes showed very significant increases and decreases in a few organisms to antibiotics of major significance. These changes are reflected in Table 3.47. and it shows that *E. cloacae*, *A. anitratus* and *X. maltophilia* are the organisms in which there are statistically significant increases over the period 1989 to 1991.

It is of major importance that antibiotics to which organisms show an increase or decrease in percent resistance, are able to be monitored for usage patterns as changes in annual resistance patterns must be accounted for. In order to do this, accurate

records of drug usage is needed and as this data was not available over this three year period, it was impossible to correlate this very important aspect of the research project.

CHAPTER 5

5. CONCLUSION

Bacterial resistance to antimicrobial agents has clinical and financial implications for the treatment of infected patients in hospitals. Over the three year period 1989 to 1991, antibiotic resistance patterns were monitored in PHPE. The changes were analysed for statistical significance and comparisons made between the whole hospital and the ICU. The ICU isolates tended to be more resistant than those from the whole hospital.

Comparisons with other studies reported from South Africa and abroad were made. Overall, PHPE's resistance figures are considered to be low and the hospital is in a fortunate position in that the resistance problem is in the early stage and with good prescribing techniques, the resistance factor can be controlled (Professor AGS Gous, Clinical Pharmacist Baragwanath Hospital : personal communication).

The development of this project's computer program for recording and analysing the results and the installation of a computer system in the microbiology department serving the hospital, has lead to a more sophisticated, user friendly, menu driven epidemiology program for handling large numbers of *in vitro* susceptibility tests performed on clinical isolates. This will enable the laboratory to accumulate a large database of local resistance patterns to the benefit of doctors, pharmacists and most important of all, the patients.

As part of this studies objectives, feedback was made to the medical staff and the observations were largely supported by the clinicians of the hospital.

It is unfortunate that a meaningful comparison between antibiotic usage and bacterial resistance could not be made. This was largely due to the fact that this area has been neglected by the hospital. Stock sheets for each ward were not accurately filled in and the manner in which the total usage was collated by the pharmacy was not easily interpreted as there are many different ways in which they recorded each item e.g. vials, boxes, tablets, suspensions, injectables. It is extremely important that this matter receive urgent attention and that one common factor be used to determine the usage either as per dose or per course.

The implications for the future are that meaningful resistance figures on a annual basis should be provided and that accurate record-keeping of total antibiotic usage and of individual wards especially the ICU should be mandatory. Decisions can thus be made as to whether there has been an over prescription or poor prescription of an antibiotic and on this basis, implement restrictions of the use of the antibiotic or 'antibiotic holidays.'

The project showed that studies of this kind undertaken on an ongoing basis can be extremely valuable in guiding clinical prescription policy. Antibiotic resistance in clinical isolates can be simply captured from pathology laboratory reports and an attempt was made to correlate changing resistance with antibiotic usage patterns in the hospital but this was precluded by inadequate pharmacy record keeping.

Correlation of the change in resistance patterns with the changes of antibiotic usage should be the special objective of a hospital Pharmaceutical and Therapeutics committee.

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