Antibacterial resistance patterns found in urine samples obtained from the elderly in Gauteng.

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Research Report Supervised

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DECLARATION

Student's contribution to article(s) and agreement of co-author(s)

I, Olivia Labuschagne, student number 1118354, declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Research Report .

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Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Title: Antibacterial resistance in urinary samples from long term care-facility and community-dwelling older people in Gauteng, South Africa

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DEDICATION

This Research Report is dedicated to my beloved husband Andries Barend Labuschagne, and my supportive parents Anton and Elsabé de Kock.

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ABSTRACT

Background:

Elderly are frequent users of healthcare services and may have complex needs related to frailty and multimorbidity. Urinary tract infection (UTI) is often diagnosed in this cohort (often based on non-specific or atypical symptoms) leading to antimicrobial therapy, often chosen empirically. This presents a poorly understood risk of antimicrobial resistance. More accurate data on antimicrobial resistance (AMR) of urinary pathogens in older people, including LTCF residents, is needed. This study aims to determine if samples obtained from LTCF-dwelling individuals show different rates of *in vitro* AMR compared to samples obtained from community dwelling older people (aged 60 years).

Methodology:

The study used computerised microbiology laboratory records of urinary samples analysed by Ampath Laboratories in South Africa. χ^2 analyses were used to detect differences in resistance patterns between LTCF and community-dwelling individuals. Sub-group analyses and multivariable logistic regression were undertaken for gender, age, in-patient and out-patient samples, and year of collection.

Results:

Microbiological results from urine samples in Gauteng where analysed (n=50,704). Three cultured bacteria (*Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis*) showed significant differences in AMR between the two study cohorts. The adjusted odd ratios for *Escherichia coli* and *Proteus mirabilis* indicated increased AMR amongst LTCF residents.

Conclusion:

Urine samples from LTCF-dwelling people have higher rates of *in vitro* resistance to common antimicrobials used to treat UTI. Greater focus on antimicrobial stewardship in LTCFs is recommended extending to diagnostic approach, empirical antibiotic choice and bacteriological confirmation of antimicrobial choice.

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LIST OF ABBREVIATIONS

AMS	Antimicrobial Stewardship
AMR	Antimicrobial Resistance
ARG	Antimicrobial Resistant Genes
CAESAR	Central Asia and Eastern Europe
CLSI	Clinical and Laboratory Standard Institute
EARS-Net	European Antimicrobial Resistance Surveillance Network
EUCAST	European Committee for Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance Surveillance System
LTCF	Long-term Care Facilities
MDRO	Multiple Drug Resistant Organism
OECD	Organisation for Economic Co-operation and Development
STG	Standard Treatment Guidelines
UTI	Urinary Tract Infection
WHO	World Health Organisation

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

The literature review will offer contextual insights into the current issue by delving into antimicrobial resistance (AMR), clarifying its significance, and highlighting its pivotal role and implications within the elderly demographic (60≥ years).

1.2 Antimicrobial resistance as a global health concern

The development of antibiotics changed modern healthcare and has saved the lives of many people since the first man-made antibacterial agent was approved for use in 1910 (Nicolaou and Rigol, 2018). Antibiotics have gone through a constant evolution to improve treatment outcomes and have included ground breaking finds such as the discovery of Penicillin by Sir Alexander Fleming (Nicolaou and Rigol, 2018). Following this discovery, Sir Alexander Fleming warned against the abuse of antibiotics and the possibility of resistance development as early as the 1940's (van Buul et al., 2012). This foreshadowing has since proven true with antimicrobial resistance (AMR) having emerged as a pressing global health concern, impacting healthcare systems worldwide (Eleraky et al., 2020; Volkov, 2024). Antimicrobial resistance places a substantial clinical and financial burden on a country (Collignon and McEwen, 2019). Resistance occurs when antimicrobials used to treat an infection lose efficacy due to intrinsic resistance (primary resistance) as well as mutations (secondary resistance) within the bacteria (Nicolaou and Rigol, 2018; Murray et al., 2022). The progression of AMR is a burgeoning causal factor in mortality, with projections suggesting it could claim the lives of 10 million people annually by 2050 (O'Neill, 2016). South Africa has not been immune to AMR as it has been observed in both the private and public healthcare sector (Manderson, 2020).

Although AMR is a problem that affects the broader population, high AMR rates are seen in vulnerable populations: hospitalised patients, immunosuppressed patients, and the elderly (O'Neill, 2016; Thornley et al., 2019).

1.3 Ageing population

In October 2022, the WHO released a report indicating that the pace of population aging has notably increased when compared to previous assessments. (WHO, 2022). As of 2020, the number of individuals aged 60 years and above surpassed that of children under the age of 5 (WHO, 2022). South Africa is also experiencing the demographic shift reported by the WHO. In South Africa, the elderly population, defined as those aged 60 years or older, accounts for 8.1% of the estimated population of 56.5 million (Stats SA, 2019).

With the increased life expectancy and growing older population the need for increased focus on the older population and its impact on healthcare in South Africa is necessary. Gerontological dependency highly impacts current and future projected health expenditure in South Africa and research estimates that the cost of public healthcare will double in the next 15 years (Tunzi and Simo-Kengne, 2020). When the impact of aging is overlooked by policy makers, inadequate resource allocation to address the challenges can lead to the older population being more vulnerable and marginalised within the community (Lopreite and Mauro, 2017). Policy making plays a big role in ensuring the wellbeing of older individuals in an aging population.

An aging population is inevitably accompanied by healthcare challenges linked to the elderly demographic.

1.4 Healthcare challenges associated with the elderly

The elderly show a decrease in overall health, associated with varying clinical factors such as an increase in comorbid conditions (such as cardiovascular disease, diabetes mellitus, arthritis) (Laudisio et al., 2017). Other health related issues such as a decrease in mobility, cognitive function auditory and visual acuity highly impact the health of the elderly (Emerson et al., 2021; Sahoo et al., 2021; Kalideen et al., 2022).

Elderly with more complex healthcare issues often stay in long-term care facilities (LTCF). A LTCF is a specialized establishment offering residents a wide range of medical and personal care services. These services include accommodation, rehabilitation, and restoration (Kalideen et al., 2022). In contrast, a community-dwelling older individual, do not have as easy access to specialised healthcare

resources (Chi et al., 2019). Infections that occur in LTCF are mostly considered to be healthcare associated infections (HAI) (Eilers et al., 2012). These HAI contribute, to a large extent, the worsening of the health status of the older demographic through increased hospital admissions and an increase in morbidity and mortality (Cairns et al., 2017). In 2019, a study in Australia investigated the socio-demographic and health service factors associated with dispensing antibiotics to the elderly and found that the highest dispensing occurred among those residing in aged care facilities (Chen et al., 2019). Treating residents of LTCFs is often difficult because they present with non-specific symptoms which could be wrongly associated with infection (Mohana Sundaram et al., 2023).

The Healthcare-associated infections in long-term care facilities (HALT) 3 study in 2017 found that the most common ailments for which antimicrobials where prescribed in LTCF in Europe were UTIs followed by respiratory tract and skin or wound infections (Ricchizzi et al., 2018). UTIs are more prevalent among the elderly population (Gravey et al., 2017), with a rising incidence in men as age advances (Baran et al., 2023; Myoung et al., 2021). Identifying UTIs in the older population, however, poses challenges due to atypical signs and symptoms of infection commonly presented by this demographic (Gravey et al., 2017; Shallcross et al., 2020a; Zeng et al., 2020a). The older population often suffer from common risk factors for developing UTI. These risk factors include: urinary incontinence, cognitive impairment, chronic indwelling catheter, diabetes mellitus and recent urologic instrumentation to name a few (Zeng et al., 2020a). UTIs in the older population, particularly those residing in LTCFs, contribute significantly to complications such as bacteraemia, hospitalization, and mortality, owing to factors such as advanced age, coexisting health conditions, limited mobility, and urinary tract interventions (Jla et al., 2021).

The complexity of treating elderly lead to high antibiotic use, in previous research found to even be as high as 4.0 to 7.3 antibiotic courses for each 1000 days for elderly who live in LTCF (van Buul et al., 2012). High antibiotic use is often associated with increased AMR.

1.5 Antimicrobial resistance amongst the older population

The inappropriate and excessive use of antibiotics stands as a pivotal factor fuelling the rise of AMR (Hansen et al., 2020). Of particular concern is the older population, characterized by a heightened prevalence of antibiotic use (Kusuma et al., 2022). Within the context of LTCFs, antibiotic overprescribing is a pervasive global challenge, driven by complex diagnostic and treatment issues arising from physiological changes, high hospital admission frequency, daily health fluctuation and the presence of multiple comorbidities associated with aging (Biguenet et al., 2023; Chen et al., 2019).

While combating antibiotic overuse is essential, it is equally imperative to recognize that the underuse of antibiotics is not a straightforward solution. Research conducted by Gharbi and colleagues in 2019 demonstrated that withholding or delaying antibiotics for older individuals with urinary tract infections (UTIs) significantly increased the odds of developing bloodstream infections and was associated with elevated mortality rates (Gharbi et al., 2019).

Several international studies have been conducted to investigate the presence of AMR in the elderly population (Pereira et al., 2016; Rivera-Izquierdo et al., 2020). Elderly amongst the older percentile of the population often show higher AMR when compared to younger populations (Ji et al., 2016). Recent studies have shown high Gram-negative AMR in LTCFs residents as high as 20-30% (Jump et al., 2017). A study conducted in Taiwan investigated the rates of (MRSA) from LTCFs and hospitals; in Changhua the MRSA rate was found to be higher than the rate found in hospitals(Hsu et al., 2021). In a Spanish case series study, which looked at early diagnosis of AMR infections through anal exudates of LTCF residents found that the prevalence of multiple drug resistant organism (MDRO) colonization was 34.5%, and alarmingly, 70% of these cases had not been previously identified in the clinical records (Rivera-Izquierdo et al., 2020). Limited information is available in South Africa regarding the prevalence of infection and AMR in the elderly and specifically in LTCFs.

Disparities in antibiotic resistance patterns among older populations have been observed globally. A Norwegian study in 2015 found no statistically significant difference in resistance patterns between LTCF residents and those living in the

community (Fagan et al., 2015) Conversely, an Australian study reported significant differences in urine bacteriology between community-dwelling individuals and LTCF residents (Xie et al., 2012). These variations underscore the heterogeneous nature of antibiotic resistance, which is further exemplified by studies on community acquired UTIs in South Africa, revealing divergent prevalence rates of *E. coli* in different regions (Fourie J L et al., 2021; Lewis et al., 2013).

As a result, AMR has been identified by the WHO as one of the biggest modern-day health concerns, emphasising the importance of combatting increasing AMR (Aslam et al., 2021).

1.6 Combatting antimicrobial resistance

Infection prevention, antimicrobial stewardship (AMS) and surveillance have been identified as crucial factors in countering AMR and plays a key role in the Global Action Plan adopted by the World Health Organisation (WHO) in 2015 (WHO, 2015; Chetty et al., 2019).

In low- and middle-income countries, effective surveillance of AMR often faces more challenges than in high-income nations (Neema et al., 2023). South Africa, categorized as an upper middle-income country, grapples with these barriers which include, major dependence on funding, inadequate laboratory infrastructure, limited personnel capacity and training, inadequate data collection systems and deficiencies in quality assurance measures (Iskandar et al., 2021; Murray et al., 2022). The importance of strengthening of AMR surveillance in low- and middle- income countries is highlighted by the fact that those countries often have a higher burden of infection, and their health systems are not able to adequately respond to the burden (Seale et al., 2017). The high burden of infection is often due to inadequate microbiological testing, inappropriate use and inadequate access to antibiotics and poor hygiene practices (Mathur et al., 2022).

The Global AMR Surveillance System (GLASS) was launched by the WHO as a first global collaborative AMR surveillance program (Neema et al., 2023). This surveillance program includes many low-, middle- as well as high-income countries, including South Africa which is considered an upper middle-income country (Iskandar et al.,

2021). Utilising surveillance networks such as European Antimicrobial Resistance Surveillance Network (EARS-Net), Central Asia and Eastern Europe (CAESAR) and Latin American (Red Latino americana de Vigilancia de la Resistencia a Los Antimicrobianos, ReLAVRA) has been a source of the greatest volume of country level data (Seale et al., 2017; Iskander et al., 2021). EARS-Net achieved a milestone in 2022 when all European Union/European Economic Area countries reported data in contribution to the annual epidemiological report (ECDC, 2023). Surveillance data from non-European and American regions have been lacking or have been underrepresented in the surveillance reports due to low country participation (Seale et al., 2017).

South Africa launched its National AMR Strategy Framework with implementation guidelines in conjunction with being enrolled in GLASS (Chetty et al., 2019). This National Action Plan sets the framework for South Africa to curb AMR utilising different strategies which include surveillance. The execution of recommended guidelines and strategies frequently falls short in practical application. A 2021 study evaluating the impact of the National AMR Strategy Framework highlighted a lack in effective multidisciplinary team collaboration, education and AMR surveillance in the Public sector mainly due to resource constraints and non-availability of the necessary microbiology (Engler et al., 2020).

Effective AMS has the capacity of reducing AMR in different healthcare settings. In North Carolina an implemented AMS program reduced the rate of AMR in urine samples (Rivera-Izquierdo et al., 2020). A scoping review on AMS in South Africa revealed that while the country possesses AMS plans in both public and private sectors, there is insufficient emphasis on their implementation (Chetty et al., 2019). Infection control is also a critical aspect of curbing AMR. Residents of LTCF often life in very close proximity which increases the difficulty of preventing the spread of infection (Arendse et al., 2022; Huang et al., 2023)

Research has shown that even though strategies to improve AMR have improved, there is still a significant knowledge gap regarding key factors such as antimicrobial research and development, drivers of AMR, AMS, infection prevention and control especially in low- and middle-income countries (Hamers et al., 2023).

1.7 Problem statement

Antimicrobial resistance reports often focus on the effect of confounders such as age, gender and health status, hospital admission on the resistance of organisms against antibiotics. The impact the living environment such as LTCF has been studied in Europe but such information for South Africa is scarce (Kusuma et al., 2022).

The lack of a proper surveillance system in key areas, such as LTCFs, hampers efforts to understand the extent of the problem related to antibiotic use and resistance (Ekwanzala et al., 2018; Ramsamy et al., 2018). Despite the importance of LTCFs for elderly populations in Africa, there is a significant gap in published literature on the standards and quality of care for elderly residents in these facilities. This is concerning given that in South Africa alone, there are approximately 1150 public and 1000 private residential LTCFs for the elderly (Arendse et al., 2022).

Overall, addressing the problem of AMR in South African LTCFs will require a concerted effort from healthcare providers, policymakers, and the public to implement effective infection control and antimicrobial stewardship measures. This study will provide information highlighting the need for proper surveillance of AMR and the impact of the living environment of the older population's resistance to antibiotics. The results will hopefully spark the conversation of sustainable change in antibiotic stewardship programs for the elderly in the context of an ageing population.

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CHAPTER 2: JOURNAL GUIDELINES TO AUTHOR

This section details the author instructions for submission to the journal *International Journal of Antimicrobial Agents*. The style and formatting of the article in Section 3 is specific to the author guidelines and may differ from the rest of the document.

2.1. Introduction

These guidelines generally follow the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals". The complete document appears at https://www.icmje.org.

2.1.1. Types of paper

The following types of manuscripts are routinely accepted (please note that word count is from abstract to references but excluding references):

2.1.1.1. Original Articles

The form of these articles is discussed fully below; an abstract is required. They should be no longer than 4000 words and 40 references (as above, please note that word count also excludes tables, figures and legends). IJAA will be happy to consider papers of veterinary origin as long as there is some linkage of the scientific work back to human antibiotic use.

2.2. Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address

2.2.1. Manuscript:

All necessary files have been uploaded:

- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided *Graphical Abstracts / Highlights files* (where applicable) *Supplemental files* (where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
- Relevant declarations of interest have been made
- Journal policies detailed in this guide have been reviewed
- Referee suggestions and contact details provided, based on journal requirements

Please ensure that the following are including in your submission: l One author designated as corresponding author: l Their E-mail address l Full postal address l Telephone and fax numbers l Keywords l Cover letter addressed to the Editor, introducing the manuscript and confirming that it is not being submitted concurrently elsewhere l All figure captions l All tables (including title, description, footnotes) l All necessary files have been uploaded as attachments to the e-mail l Manuscript has been spell checked l All text pages have been numbered l References are in the correct format for this journal l All references mentioned in the Reference list are cited in the text and vice versa l Permission has been obtained for use of copyrighted material from other sources (including the Web).

2.3. Before you begin

2.3.1. Ethics in publishing

Please see our information on Ethics in publishing.

If your study involves sequences, it is compulsory for you to confirm where you have deposited these (please include the deposit ID and the relevant database link) during the submission process.

2.3.2. Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

The author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committee(s). This statement should contain the date and reference number of the ethical approval(s) obtained. Authors should also include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

The journal will not accept manuscripts that contain data derived from unethically sourced organs or tissue, including from executed prisoners or prisoners of conscience, consistent with recommendations by Global Rights Compliance on Mitigating Human Rights Risks in Transplantation Medicine. For all studies that use human organs or tissues authors must provide sufficient evidence that they were procured in line with WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation. The source of the organs or tissues used in clinical research must be transparent and traceable. Authors of manuscripts describing organ transplantation must additionally declare within the manuscript:

1. that autonomous consent free from coercion was obtained from the donor(s) or their next of kin; and
2. that organs/tissues were not sourced from executed prisoners or prisoners of conscience.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Research Council's Guide for the Care and Use of Laboratory Animals and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

2.3.3. Informed consent and patient details

Studies on patients or volunteers (including organ/tissue donors) require informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author, but copies should not be provided to the journal.

Only if specifically requested by the journal in exceptional circumstances (for example if a legal issue arises) the author must provide copies of the consents or evidence that such consents have been obtained. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals. Unless the author has written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

2.3.4. Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double anonymized) or the manuscript file (if single anonymized). If there are no interests to declare then please state this: 'Declarations of interest: none'. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches.

2.3.5. Declaration of generative AI in scientific writing

The below guidance only refers to the writing process, and not to the use of AI tools to analyse and draw insights from data as part of the research process.

Where authors use generative artificial intelligence (AI) and AI-assisted technologies in the writing process, authors should only use these technologies to improve readability and language. Applying the technology should be done with human oversight and control, and authors should carefully review and edit the result, as AI can generate authoritative-sounding output that can be incorrect, incomplete or biased. AI and AI-assisted technologies should not be listed as an author or co-author, or be cited as an author. Authorship implies responsibilities and tasks that can only be attributed to and performed by humans, as outlined in Elsevier's AI policy for authors. Authors should disclose in their manuscript the use of AI and AI-assisted technologies in the writing process by following the instructions below. A statement will appear in the published work. Please note that authors are ultimately responsible and accountable for the contents of the work.

2.3.5.1. Disclosure instructions

Authors must disclose the use of generative AI and AI-assisted technologies in the

writing process by adding a statement at the end of their manuscript in the core manuscript file, before the References list. The statement should be placed in a new section entitled ‘Declaration of Generative AI and AI-assisted technologies in the writing process’.

Statement: During the preparation of this work the author(s) used [NAME TOOL / SERVICE] in order to [REASON]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

This declaration does not apply to the use of basic tools for checking grammar, spelling, references etc. If there is nothing to disclose, there is no need to add a statement.

2.3.6. Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify compliance, your article may be checked by Crossref Similarity Check and other originality or duplicate checking software.

2.3.7. Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias,

stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

2.3.8. Reporting sex- and gender-based analyses

2.3.8.1. Reporting guidance

For research involving or pertaining to humans, animals or eukaryotic cells, investigators should integrate sex and gender-based analyses (SGBA) into their research design according to funder/sponsor requirements and best practices within a field. Authors should address the sex and/or gender dimensions of their research in their article. In cases where they cannot, they should discuss this as a limitation to their research's generalizability. Importantly, authors should explicitly state what definitions of sex and/or gender they are applying to enhance the precision, rigor and reproducibility of their research and to avoid ambiguity or conflation of terms and the constructs to which they refer (see Definitions section below). Authors can refer to the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER guidelines checklist. These offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting and research interpretation - however, please note there is no single, universally agreed-upon set of guidelines for defining sex and gender.

2.3.8.1.1. Definitions

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth (""sex assigned at birth""), most often based solely on the visible external anatomy of a newborn. Gender generally refers to socially constructed roles, behaviors, and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man) and unchanging whereas these constructs actually exist along a spectrum and include additional sex categorizations and gender identities such as people who are intersex/have differences of sex development (DSD) or identify as non-binary. Moreover, the terms ""sex"" and ""gender"" can be ambiguous—thus it is important for authors to define the manner in which they are used. In addition to this definition guidance and the SAGER guidelines, the resources on this page offer further insight around sex and gender in research studies.

2.4. Contributors

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CHAPTER 3: DRAFT ARTICLE

Antibacterial resistance in urinary samples from long term care-facility and community-dwelling older people in Gauteng, South Africa

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Keywords:
Antimicrobial resistance, long-term care facility, urinary tract infection, surveillance, elderly

Highlights:

- Urinary tract infection is a common clinical diagnosis in older people.
- Antibiotics are used excessively in the elderly
- Where a patient lives has an impact on antimicrobial resistance
- Long-term care facility residents have higher antimicrobial resistance rates
- Long-term care facilities require an enhanced approach to infection prevention and control.

Abstract:

Background:

Elderly are frequent users of healthcare services and may have complex needs related to frailty and multimorbidity. Urinary tract infection (UTI) is often diagnosed in this cohort (often based on non-specific or atypical symptoms) leading to antimicrobial therapy, often chosen empirically. This presents a poorly understood risk of antimicrobial resistance. More accurate data on antimicrobial resistance (AMR) of urinary pathogens in older people, including LTCF residents, is needed. This study aims to determine if samples obtained from LTCF-dwelling individuals show different rates of *in vitro* AMR compared to samples obtained from community dwelling older people (aged 60 years).

Methodology:

The study used computerised microbiology laboratory records of urinary samples analysed by Ampath Laboratories in South Africa. χ^2 analyses were used to detect differences in resistance patterns between LTCF and community-dwelling individuals. Sub-group analyses and multivariable logistic regression were undertaken for gender, age, in-patient and out-patient samples, and year of collection.

Results:

Microbiological results from urine samples in Gauteng where analysed (n=50,704). Three cultured bacteria (*Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis*) showed significant differences in AMR between the two study cohorts. The adjusted odd ratios for *Escherichia coli* and *Proteus mirabilis* indicated increased AMR amongst LTCF residents.

Conclusion:

Urine samples from LTCF-dwelling people have higher rates of *in vitro* resistance to common antimicrobials used to treat UTI. Greater focus on antimicrobial stewardship in LTCFs is recommended extending to diagnostic approach, empirical antibiotic choice and bacteriological confirmation of antimicrobial choice.

1. Introduction

Antimicrobial resistance (AMR) has emerged as a pressing global health concern, impacting healthcare systems worldwide (Eleraky et al., 2020; Volkov, 2024). This issue resonates strongly in South Africa, where a noticeable surge in antibiotic use and resistance has been observed across both private and public healthcare sectors (Manderson, 2020). Infection prevention, antimicrobial stewardship (AMS) and surveillance methods are critical factors in countering rising AMR (Chetty et al., 2019).

A report published by the World Health Organisation (WHO) in October 2022 stated that compared to the past, the pace of population ageing has accelerated significantly (WHO, 2022). An ageing population is inevitably accompanied by associated healthcare challenges linked to an increased antibiotic use (Kusuma et al., 2022). With the population steadily aging, the demand for long-term care facilities (LTCF) has also risen. A LTCF is a specialized centre providing residents with comprehensive medical and personal care services. These services encompass accommodation, rehabilitation, and restoration (Kalideen et al., 2022). In contrast, a community-dwelling older individual, do not have as easy access to healthcare resources and often only seek out help if they develop disease (Chi et al., 2019). These differences, combined with higher rates of frailty and other long-term conditions may lead to a higher use of antibiotics within LTCF.

The inappropriate and excessive use of antibiotics stands as a pivotal factor fuelling the rise of AMR (Hansen et al., 2020). Antibiotic overprescribing is a pervasive global challenge, driven by complex diagnostic and treatment issues arising from physiological changes, high hospital admission frequency, and the presence of multiple comorbidities associated with aging especially seen in LTCF residents (Biguenet et al., 2023; Chen et al., 2019; Kusuma et al., 2022). The most common ailments for which antimicrobials are prescribed in LTCF in Europe are UTIs followed by respiratory tract and skin or wound infections (Ricchizzi et al., 2018). Infections of the urinary tract are prevalent among the older population, with a rising incidence in men as age advances (Baran et al., 2023). Identifying UTIs in the elderly poses challenges due to atypical signs and symptoms of infection commonly presented by this cohort (Shallcross et al., 2020a; Zeng et al., 2020a). This population often suffers

from common risk factors for developing UTI including urinary incontinence, cognitive impairment, chronic indwelling catheter, and diabetes mellitus to name a few (Zeng et al., 2020a). In the older population, particularly those residing in LTCFs, UTIs contribute significantly to complications such as bacteraemia, hospitalization, and mortality; owing to factors such as advanced age, coexisting health conditions, limited mobility, and urinary tract interventions (Jla et al., 2021). The presence of asymptomatic bacteriuria in this cohort increases the difficulty to accurately diagnose UTIs.

In addition, disparities in antibiotic resistance patterns in samples from older populations have been observed globally. A Norwegian study in 2015 found no statistically significant difference in resistance patterns between nursing home residents and those living in the community (Fagan et al., 2015) Conversely, an Australian study reported significant differences in urine bacteriology between community-dwelling individuals and LTCF residents (Xie et al., 2012). These variations underscore the heterogeneous nature of antibiotic resistance, which is further exemplified by studies on community acquired UTIs in South Africa, revealing divergent prevalence rates of *E. coli* in different regions (Fourie J L et al., 2021; Lewis et al., 2013).

Notably, there is a dearth of information concerning infection prevalence and AMR in LTCFs in South Africa, despite the presence of approximately 1150 public and 1000 private residential LTCFs for the older population (Arendse et al., 2022). This knowledge gap is alarming, especially considering that antibiotic resistance compromises healthcare professionals' ability to effectively treat infections (Sekyere, 2016). The absence of a robust surveillance system, particularly in LTCFs, impedes efforts to comprehend the extent of the antibiotic use and resistance dilemma (Ekwanzala et al., 2018; Ramsamy et al., 2018). Establishing a comprehensive surveillance mechanism could facilitate a critical evaluation of current empiric antibiotic treatments, paving the way for necessary adjustments. As we navigate the complex landscape of antibiotic resistance and an aging population, ensuring judicious antibiotic use is paramount for treatment success and the prevention of complications, underscoring the urgency of addressing the antibiotic resistance predicament.

Reports concerning AMR frequently focus on the influence of covariates such as age, gender, health status and hospital admission on the development of AMR. While the impact of living environments like LTCFs has been studied in Europe, there is a scarcity of such information available for South Africa (Kusuma et al., 2022). This research study investigates the impact of the living environment of the older population's resistance to antibiotics for a common ailment such as a UTI .

2. Methodology

2.1 Study design and setting

This was a retrospective, epidemiological, observational study using anonymised data, stored routinely in computerised microbiology laboratory records of Ampath Laboratories, South Africa. Ampath Laboratories is one of South Africa's foremost pathology laboratories, serving about 40% of the South African healthcare sector, with > 350 laboratories and collection centres nationwide. Clinical microbiology test results of bacterial isolates, obtained from LTCF and community sites located in Gauteng, during the period of January 2018 to September 2023, were selected for analysis. This study was approved by the University of Witwatersrand Human Ethics Committee (HREC) Waiver number M230669 MED23-06-154.

The following agents were selected as antibiotics of interest: ciprofloxacin, gentamicin, fosfomycin, nitrofurantoin, ceftriaxone, amoxicillin/clavulanic acid and co-trimoxazole. Of these, ciprofloxacin, gentamicin, fosfomycin and nitrofurantoin are included in the South African Standard Treatment Guidelines (STG) for the treatment of complicated and uncomplicated UTI (*Standard Treatment Guidelines and Essential Medicines List for South Africa*, 2020). Ceftriaxone is included in the hospital level STG for acute pyelonephritis (if impaired renal function) and was decided to be included in our analysis. However, Ampath is predominantly accessed by the private sector which is not held to the expectations of the STG. Amoxicillin/clavulanic acid and co-trimoxazole were included based on standard practice and as a result of their inclusion in global treatment guidelines.

2.2 Participant population

Inclusion criteria for analysis were: (i) urinary samples from participants aged ≥60 years at the time of sampling; (ii) monomicrobial and polymicrobial isolates; (iii) bacterial isolates. This study focused on bacteria cultured in urine samples and therefore non-bacterial isolates were excluded. To reduce the risk that complex or resistant infections were over-represented, any repeated isolates from the same participant and sample site (urine) within a 12-week period were excluded (as complex and/or nosocomial infections would tend to be sampled more frequently during treatment episodes). Records containing missing data pertaining to the microbiological test result or living environment of the patient were excluded. This included samples where the address on record was only a postal address and therefore not possible to classify the patient as LTCF or community dwelling.

2.3 Sample processing and analysis:

In 2018, Ampath laboratories utilised Clinical and Laboratory Standard Institute (CLSI) breakpoints to interpret susceptibility results. When analysing urine samples, if the white blood cell count was ≥ 20 cells/μl, direct sensitivity tests were conducted using the laboratory's protocol disc dispensations. If the white blood cell criteria were not met, then sample culture was to be completed. In 2019, however, Ampath changed their protocol and started using the European Committee for Antimicrobial Susceptibility Testing (EUCAST) interpretive breakpoints. This change was in accordance with the European Commissions enacted legislation to advocate for the use of EUCAST (Karagiannidou et al., 2023). Although both EUCAST and CLSI are accepted on a global research front, the interpretive guidelines do contain important differences(Najeeb et al., 2021). A study comparing resistance rates obtained from using both breakpoints found discrepancies and higher resistance rates for some antibiotics such as Ciprofloxacin when EUCAST breakpoints where utilised (Cusack et al., 2019).

2.4 Data processing and classification

All participant identifiable variables were anonymised within Ampath before the dataset was shared. The following data were collected: (i) microscopy, sensitivity and

culture results: (ii) Participant details including age and sex assigned at birth, (iii) Clinical facility location (from where the sample was sent), (iv) Sample requisition number, (v) Date of sampling, (vi) Doctor copy number (doctor reference number to ensure results are forwarded to the doctor). Data processing and classification were conducted using Microsoft Excel. Samples were classified as being from 'community-dwelling' or 'LTCF-dwelling' individuals according to the patient's residential status when samples were collected. The South African care system includes retirement villages which contain co-located facilities offering incremental care and healthcare as residents become more frail. These were included in the LTCF group in our analysis. To identify LTCF samples, a reference list of LTCFs within Gauteng Province was formulated and patient addresses matched against this list. The remaining samples were manually screened for other LTCF samples if they met any of the following criteria (i) addresses containing terms indicative of a LTCF (including the terms frail, retire, old age, senior, assisted living); (ii) records from addresses linked to samples from > 2 distinct patients; (iii) records with doctor copy numbers associated with the LTCF reference list.

2.5 Statistical analysis

Statistical analysis was performed using Stata release 18 (StataCorp, 2023). Intermediate antibiotic resistance results were classified with sensitive results, to enable dichotomous analysis, as the bacteria are still sensitive to such an agent but only at a higher dose. To compare resistance proportions between the LTCF and community-dwelling groups, odds ratios (OR) and χ^2 coefficients were calculated with a significance threshold of $p < 0.05$. The following covariables were identified in the data: age, gender, in-patient vs out-patient status and year of sampling. To adjust for potential confounding effects of co-variables, multivariable logistic regressions were used to calculate adjusted odds ratios. To assess the change in antibiotic resistance from 2018 to 2023, Kendall's tau-b correlation coefficient was used. Kendall's tau-b is a non-parametric measure of association that evaluates the strength and direction of monotonic relationships between two variables. For this analysis the two variables are antibiotic resistance and year of sampling.

3. Results

3.1 Patient demographics

In this study, data from 50,704 urine samples was analysed. The dataset represented community-dwelling individuals, comprising 81.19% (n=41,161) of the samples, with the remaining 18.81% (n=9543) originating from LTCFs. Notably, gender distribution revealed a higher prevalence of females, constituting 70.37% (n=35679) of the cohort, while males accounted for 29.63% (n=15025). The mean age of the participants at sampling was 75.48 years (SD 9.01). Residents from LTCF were older (mean age 81.67 (SD 7.77)) in comparison to the community dwelling group (mean age 74.05 (SD 8.67)). Out-patient samples accounted for 63.18% (n=32,036) of the data and in-patient samples 36.82% (n=18,668).

3.2 Identified microbial isolates from urine samples

The five most common isolates were *Escherichia coli*, predominantly representing 55.14% of the isolates identified (n=27,957), followed by *Klebsiella pneumoniae* at 17.56% (n=8,904). *Enterococcus faecalis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*, representing 5.15% (n=2,611), 4.90% (n=2,482), and 4.50% (n=2,278) respectively. Of the other bacterial species isolated, none contributed to more than 4% of the dataset. The same five pathogens occurred most commonly in both the community and LTCF dwelling groups, but with different proportions in the two groups. *P. mirabilis and P. aeruginosa* represented a higher proportion of LTCF samples compared to community dwelling samples; and *E faecalis* represented a higher proportion of the community samples (**Table 1**).

Table 1: Proportions of isolated micro-organisms per study cohort

	Overall	LTCF	Community
Escherichia coli	55.14%	55.41%	55.07%
Klebsiella pneumoniae	17.56%	16.78%	17.74%
Enterococcus faecalis	5.15%	4.15%	5.38%
Proteus mirabilis	4.90%	6.68%	4.48%
Pseudomonas aeruginosa	4.50%	5.51%	4.26%

3.3 Susceptibility and resistance results

The results of χ^2 and multivariable logistic regression comparing AMR between samples from LTCF- and community-dwelling older people for chosen antimicrobials are shown in **Table 2.**

Table 2: Overall resistance analysis per micro-organism isolated

		Ciprofloxacin	Gentamicin	Fosfomycin	Nitrofurantoin	Ceftriaxone	Amoxicillin/ Clavulanic acid	Co-trimoxazole
E. coli **(n= 27 957)**	**Number of times tested**	27 933	27 151	27 720	27 826	27 937	27 924	27 855
	#OR (95% CI)	1.246 (1.169-1.327)	0.973 (0.880-1.076)	1.349 (1.163-1.564)	1.553 (1.378-1.750)	1.236 (1.141-1.340)	1.115 (1.045-1.190)	1.057 (0.995-1.123)
	P-value	<0.001	0.596	<0.001	<0.001	<0.001	0.001	0.070
	Adjusted OR	1.172 (1.095-1.255)	0.997 (0.896-1.109)	1.151 (0.984-1.347)	1.263 (1.112-1.435)	1.259 (1.155-1.373)	1.151 (1.073-1.234)	1.099 (1.031-1.172)
	Regression P-value	<0.001	0.949	0.078	<0.001	<0.001	<0.001	0.004
K. pneumoniae **(n= 8 904)**	**Number of times tested**	8 894	8 648	8 762	8 791	8 885	8 896	8 866
	#OR (95% CI)	0.888 (0.796-0.991)	0.878 (0.781-0.986)	0.973 (0.869-1.090)	1.060 (0.946-1.187)	0.786 (0.705-0.878)	0.782 (0.700-0.873)	1.031 (0.992-1.152)
	P-value	0.032	0.026	0.631	0.307	<0.001	<0.001	0.589
	Adjusted OR	1.032 (0.916-1.161)	1.028 (0.908-1.165)	0.997 (0.880-1.130)	1.106 (0.981-1.247)	0.934 (0.828-1.053)	0.932 (0.826-1.052)	1.122 (0.996-1.265)
	Regression P-value	0.612	0.661	0.963	0.099	0.264	0.253	0.057
E. faecalis **(n= 2 611)**	**Number of times tested**	2 606		634	2 605		639	
	#OR (95% CI)	0.952 (0.656-1.353)		0.650 (0.071-2.864)	*		*	
	P-value	0.779		0.568	0.080		0.523	
	Adjusted OR	0.885 (0.612-1.279)		$	$		$	
	Regression P-value	0.516		$	$		$	
P. mirabilis **(n= 2 482)**	**Number of times tested**	2 481	2 423	2 463	2 470	2 478	2 462	634
	#OR (95% CI)	2.164 (1.706-2.739)	1.638 (1.265-2.112)	1.720 (1.380-2.140)	1.130 (0.700-1.885)	1.134 (0.736- 1.714)	1.155 (0.907-1.465)	1.490 (1.238-1.795)
	P-value	<0.001	<0.001	<0.001	0.607	0.540	0.225	<0.001
	Adjusted OR	1.875 (1.465-2.400)	1.687 (1.292-2.203)	1.519 (1.208-1.910)	1.240 (0.758-2.029)	1.161 (0.757-1.779)	1.074 (0.839-1.376)	1.539 (1.269-1.868)
	Regression P-value	<0.001	<0.001	<0.001	0.391	0.494	0.571	<0.001
P. aeruginosa **(n= 2 278)**	**Number of times tested**	2 274	2 113	1 423	1 154	172	70	342
	#OR (95% CI)	1.147 (0.918-1.430)	0.857 (0.660-1.107)	1.007 (0.767-1.317)	0.650 (0.259-1.773)	0.484 (0.153-1.711)	1.125 (0.084-62.290)	1.624 (0.774-3.666)
	P-value	0.213	0.227	0.958	0.321	0.172	0.921	0.178
	Adjusted OR	1.323 (1.045-1.676)	1.074 (0.819-1.410)	0.985 (0.738-1.315)	0.484 (0.189-1.241)	0.459 (0.135-1.554)	0.347 (0.020-6.013)	2.091 (0.942-4.641)
	Regression P-value	0.020	0.606	0.919	0.131	0.210	0.467	0.070

#OR >1 indicates increased odds of AMR to agent in LTCF group, while OR <1 increased odds in community-dwelling group.

Susceptibility to these antimicrobials was not tested.

$ multivariable regression not appropriate due to collinearity of co-variates.

** Exact confidence levels not possible with zero count cells.*

.

The following antibiotics showed increased resistance in *E.coli* samples obtained from LTCF-dwelling according to $\chi^2$and OR analysis: ciprofloxacin (OR = 1.246, 95% CI 1.169-1.327, p<0.001), fosfomycin (OR = 1.349, 95% CI 1.163-1.564, p<0.001), nitrofurantoin (OR = 1.553, 95% CI 1.378-1.750, p<0.001), ceftriaxone (OR = 1.236, 95% CI 1.141-1.340, p<0.001) and amoxicillin/clavulanic acid (OR = 1.115, 95% CI 1.045-1.190, p = 0.001) (**Table 2**). Multivariable logistic regression adjusting for gender, age, in-patient *vs* outpatient samples and year of collection, show adjusted odds ratios with increased resistance in the LTCF group for 6 of the antibiotics. The regression P-value differ slightly from the p-values obtained from χ^2analysis. Fosfomycin no longer shows statistical significance (p<0.001 vs p=0.078) while co-trimoxazole now indicates statistical significance (p=0.070 vs p=0.004) (**Table 2**).

Klebsiella pneumoniae isolates delivered statistically significant p-values for χ^2 analysis, but OR indicating higher resistance from the community-dwelling cohort, for the antibiotics ciprofloxacin (OR =0.888, 95% CI 0.796-0.991, p=0.032), gentamicin (OR = 0.878, 95% CI 0.781-0.986), ceftriaxone (OR = 0.786, 95% CI 0.705-0.878, p<0.001) and amoxicillin/clavulanic acid (OR = 0.782, 95% CI 0.700-0.873, p<0.001) (**Table 2**). However, these differences did not persist in multivariable logistic regression with no results reaching statistical significance.

Enterococcus faecalis isolates indicated no statistically significant differences between the community and LTCF-dwelling groups in χ^2 analysis. Multivariable logistic regression was not possible for the majority of antibiotics due to collinearity of the co-variates (**Table 2**).

Proteus mirabilis isolates delivered statistically significant results for ciprofloxacin (OR = 2.164, 95% CI 1.706-2.739, p<0.001), gentamicin (OR = 1.638, 95% CI 1.265-2.112, p<0.001) , fosfomycin (OR = 1.720, 95% CI 1.380-2.140, p<0.001) and co-trimoxazole (OR = 1.490, 95% CI 1.238-1.795) when comparing the two study cohorts by means of χ^2 analysis. The Odds ratio indicated more resistant results from LTCF samples (**Table 2**)**.** Multivariable logistic regression did not impact the results obtained from χ^2analysis.

Pseudomonas aeruginosa isolates did not deliver statistically significant p-values when comparing the two study cohort by means of χ^2 analysis. Multivariable logistic regression did however deliver a statistically significant p-value for ciprofloxacin (Adjusted OR = 1.323, 95% CI 0.918-1.430, p=0.020) and an adjusted odds ratio favouring resistance in LTCFs (**Table 2**)**.**

3.4 Antimicrobial Resistance Trend Analysis

Trend analysis investigated if AMR patterns change over time when comparing the values of the LTCF to the community cohort. *Escherichia coli* isolates delivered a statistically significant positive trend result for fosfomycin (LTCF: τ_B: 0.035, p=0.004; Community: τ_B: 0.027, p<0.001) and ceftriaxone (Community: τ_B: 0.033, p<0.001) indicating an increase in resistance over time (**Table 3**). E.*coli* isolates showed a steady increase of fosfomycin resistance in both cohort (LTCF: 3.74% (2018) to 6.18%(2023); Community: 2.75% (2018) to 3.74%(2023)).

Table 3: *Escherichia coli* trend analysis

	***E.coli* (n= 27 957)**							
	Kendall's Tau-B correlation coefficient	**Kendall's Tau P-value**	**% Resistance 2018**	**% Resistance 2019**	**% Resistance 2020**	**% Resistance 2021**	**% Resistance 2022**	**% Resistance 2023**
LTCF								
Ciprofloxacin	-0.051	<0.001	40.13	35.65	35.13	34.4	35.4	30.71
Gentamicin	-0.011	0.388	9.26	11.9	12.05	10.19	10.48	8.66
Fosfomycin	**0.035**	**0.004**	**3.74**	**3.99**	**4.12**	**5.63**	**5.27**	**6.18**
Nitrofurantoin	-0.053	<0.001	10.02	8.75	7.72	7.37	6.5	4.86
Ceftriaxone	0.003	0.831	17.64	18.19	16.69	17.4	17.19	18.9
Amoxicillin/ Clavulanic acid	-0.058	<0.001	38.61	33.04	30.59	28.92	27.88	30.05
Co-trimoxazole	-0.010	0.430	48.01	52.86	49.74	49.67	48.9	48.29
Community								
Ciprofloxacin	-0.029	<0.001	33.62	32.02	29.61	29.47	29.94	28.82
Gentamicin	-0.006	0.311	10.61	11.33	11.06	10.87	9.9	10.74
Fosfomycin	**0.027**	**<0.001**	**2.75**	**3.1**	**3.23**	**3.64**	**4**	**4.5**
Nitrofurantoin	-0.044	<0.001	6.83	5.78	6.32	3.99	4.2	3.63
Ceftriaxone	**0.033**	**<0.001**	**13.32**	**13.52**	**14.27**	**14.43**	**15.52**	**17.6**
Amoxicillin/ Clavulanic acid	-0.026	<0.001	34.21	30.37	28.11	25.89	27.88	30.24
Co-trimoxazole	-0.013	0.024	49.01	50.5	47.76	46.99	48.22	47.43

Bold: Values depicted in bold indicate statistically significant p-values with a positive Kendall's tau-b correlation coefficient indicating an increase in antibiotic resistance over time

Klebsiella pneumoniae isolates delivered a statistically significant positive trend result for fosfomycin (LTCF: τ_B: 0.209, p>0.001; Community: τ_B: 0.282, p<0.001) with a resistance increase from 25.94% (2018) to 59.68% (2023) in LTCF and from 16.19% (2018) to 64.08% (2023) in the community cohort (**Table 4**). In 2018 fosfomycin had a higher resistance rate in the LTCF cohort but in 2023 the resistance rate was higher in the community cohort.

Table 4: *Klebsiella pneumoniae* trend analysis

	***K.pneumoniae* (n=8 904)**							
	Kendall's Tau-B correlation coefficient	**Kendall's Tau P-value**	**% Resistance 2018**	**% Resistance 2019**	**% Resistance 2020**	**% Resistance 2021**	**% Resistance 2022**	**% Resistance 2023**
LTCF								
Ciprofloxacin	-0.016	0.476	48.92	50.99	46.78	49.58	52.61	47.79
Gentamicin	-0.013	0.576	35.97	37.04	34.33	34.32	39.6	31.73
Fosfomycin	**0.209**	**<0.001**	**25.94**	**27.04**	**40.09**	**38.89**	**49.19**	**59.68**
Nitrofurantoin	-0.048	0.031	63.97	62.89	67.24	57.94	57.43	57.66
Ceftriaxone	0.004	0.860	50	46.61	43.78	46.19	49.4	49.4
Amoxicillin/ Clavulanic acid	-0.006	0.772	58.99	54.08	49.79	52.97	58.57	55.02
Co-trimoxazole	-0.009	0.678	59.71	59.83	57.51	58.47	58.57	58.47
Community								
Ciprofloxacin	-0.008	0.402	49.28	54.09	54.94	51.16	52.65	52.66
Gentamicin	-0.007	0.493	37.25	41.63	38.67	38.35	37.65	38.27
Fosfomycin	**0.282**	**<0.001**	**16.19**	**24.28**	**40.77**	**40.09**	**49.86**	**64.08**
Nitrofurantoin	-0.067	<0.001	61.72	64.86	66.47	57.5	56.21	53.88
Ceftriaxone	0.004	0.684	52.63	55.24	53.57	50.56	53.93	54.9
Amoxicillin/ Clavulanic acid	0.004	0.661	60.61	63.64	59.89	55.94	60.61	64.03
Co-trimoxazole	0.006	0.565	58.45	57.95	57.09	56.51	59.41	58.82

Bold: Values depicted in bold indicate statistically significant p-values with a positive Kendall's tau-b correlation coefficient indicating an increase in antibiotic resistance over time

Enterococcus faecalis isolates did not show a trend of increased antibiotic resistance for any of the antibiotics of interest (**Table 5**).

Table 5: *Enterococcus faecalis* trend analysis

	***E. faecalis* (n=2 611)**							
	Kendall's Tau-B correlation coefficient	**Kendall's Tau P-value**	**% Resistance 2018**	**% Resistance 2019**	**% Resistance 2020**	**% Resistance 2021**	**% Resistance 2022**	**% Resistance 2023**
LTCF								
Ciprofloxacin	-0.083	0.062	18.97	12.26	5.56	8.16	6.85	10.71
Fosfomycin	0.009	0.936	1.75	2.00	0	0	0	0
Nitrofurantoin	0.000	1.000	1.05	0	0	0	0	0
Amoxicillin/ Clavulanic acid	0.000	1.000	0	0	0	0	0	0
Community								
Ciprofloxacin	-0.068	<0.001	15.34	13.04	10.84	10.70	8.09	8.39
Fosfomycin	0.003	0.955	2.81	2.90	0	0	0	0
Nitrofurantoin	-0.027	0.147	1.23	1.08	0.60	0.80	0.25	0.65
Amoxicillin/ Clavulanic acid	0.077	0.076	0	0.97	0	0	0	0

Bold: Values depicted in bold indicate statistically significant p-values with a positive Kendall's tau-b correlation coefficient indicating an increase in antibiotic resistance over time

Proteus mirabilis isolates delivered a statistically significant positive trend result for fosfomycin (Community: τ_B: 0.094, p>0.001) and amoxicillin/ clavulanic acid (Community: τ_B: 0.044, p=0.033). The LTCF cohort did not indicate a statistically significant increase in resistance over time. In 2018 fosfomycin had a higher resistance rate for the LTCF cohort, but in 2023 the community-dwelling cohort's resistance surpassed the LTCF cohort (**Table 6**).

Table 6: *Proteus mirabilis* trend analysis

	P. mirabilis (n=2 482)							
	Kendall's Tau-B correlation coefficient	Kendall's Tau P-value	% Resistance 2018	% Resistance 2019	% Resistance 2020	% Resistance 2021	% Resistance 2022	% Resistance 2023
LTCF								
Ciprofloxacin	-0.077	0.210	34.26	26.83	18.18	16.84	21.19	21.28
Gentamicin	-0.042	0.235	19.44	22.00	20.20	16.84	16.10	15.96
Fosfomycin	0.022	0.536	23.15	26.83	29.59	21.05	34.19	23.66
Nitrofurantoin	-0.025	0.484	98.15	95.12	96.91	96.84	94.07	96.81
Ceftriaxone	0.031	0.380	2.78	4.07	11.11	5.26	3.39	7.53
Amoxicillin/ Clavulanic acid	0.016	0.641	15.09	19.51	25.25	15.96	18.64	20.21
Co-trimoxazole	-0.076	0.030	56.07	52.85	57.14	44.21	44.07	46.24
Community								
Ciprofloxacin	0.017	0.630	13.89	14.19	10.34	13.81	10.56	11.68
Gentamicin	-0.016	0.451	11.55	10.89	12.41	16.57	11.70	8.28
Fosfomycin	**0.094**	**<0.001**	**7.66**	**16.32**	**17.83**	**17.45**	**19.61**	**23.88**
Nitrofurantoin	-0.029	0.166	96.43	96.18	96.86	96.12	93.87	95.49
Ceftriaxone	0.026	0.214	1.59	4.88	5.17	7.73	4.16	4.83
Amoxicillin/ Clavulanic acid	**0.044**	**0.033**	**12.55**	**18.60**	**14.53**	**16.34**	**18.49**	**20.42**
Co-trimoxazole	-0.003	0.882	39.84	44.37	37.59	39.23	39.55	41.72

Bold: Values depicted in bold indicate statistically significant p-values with a positive Kendall's tau-b correlation coefficient indicating an increase in antibiotic resistance over time

Pseudomonas aeruginosa isolates delivered a statistically significant positive trend result for fosfomycin (LTCF: τ_B: 0.167, p<0.001; Community: τ_B: 0.206, p<0.001) (**Table 7**).

Table 7: *Pseudomonas aeruginosa* trend analysis

	***P. aeruginosa* (n= 2 278)**							
	Kendall's Tau-B correlation coefficient	**Kendall's Tau P-value**	**% Resistance 2018**	**% Resistance 2019**	**% Resistance 2020**	**% Resistance 2021**	**% Resistance 2022**	**% Resistance 2023**
LTCF								
Ciprofloxacin	-0.072	0.062	35.92	32.48	21.52	34.18	20.78	27.54
Gentamicin	-0.083	0.039	27.18	20.75	15.19	19.23	18.18	12.77
Fosfomycin	**0.167**	**<0.001**	**21.05**	**28.41**	**25.00**	**29.55**	**48.89**	**47.22**
Nitrofurantoin	-0.056	0.288	100.00	95.38	97.50	100.00	92.86	97.06
Ceftriaxone	-0.239	0.148	90.91	70.00	100.00	100.00	50.00	0
Amoxicillin/ Clavulanic acid	0.155	0.575	92.31	100.00	100.00	0	0	0
Co-trimoxazole	-0.261	0.004	100.00	75.00	100.00	87.50	81.82	70.00
Community								
Ciprofloxacin	-0.059	0.005	35.71	25.57	28.09	25.00	25.07	22.22
Gentamicin	-0.029	0.190	26.91	19.88	22.41	26.07	21.53	16.00
Fosfomycin	**0.206**	**<0.001**	**17.39**	**20.65**	**31.82**	**32.70**	**49.12**	**41.94**
Nitrofurantoin	-0.022	0.467	97.76	98.81	98.00	99.32	98.37	95.40
Ceftriaxone	-0.228	0.006	95.65	92.45	80.00	100.00	60.00	33.33
Amoxicillin/ Clavulanic acid	-0.246	0.070	96.67	100.00	100.00	0	66.67	100
Co-trimoxazole	-0.174	0.003	95.24	70.37	76.47	86.21	76.67	66.67

4. Discussion

This study aimed to identify if the living environment of elderly has an impact on urine samples' *in vitro* resistance to antibiotics. The differences between resistance rates of isolates obtained from the two study cohorts were statistically significant with resistance favouring LTCF *vs.* community. The top five cultured isolates are common UTI isolates and are often the most prominent isolates in research with differing incidences but *E.coli* is often the most common (Gravey et al., 2017; Laudisio et al., 2017; Mathur et al., 2022). For both study cohort the most common isolated organism was *E.coli.* This highlights the importance of AMR surveillance to ensure understanding

of resistance patterns to reduce the change of treatment failure and increased resistance against the most common micro-organisms.

4.1 Key findings

Our study shows that, for many of the common pathogens, *in vitro* resistance to commonly recommended antimicrobials is significantly greater in samples from LTCF-dwelling residents than from their community-dwelling counterparts. This is similar to an Australian study with 4044 samples which also showed a statistically significant difference (Xie et al., 2012) but differs from a smaller Norwegian study from 2015 with a total of 3786 samples which found no statistically significant difference between the two groups (Fagan et al., 2015). The persistence of significant differences in the adjusted analyses suggest that this cannot be explained solely by factors such as age, gender, in-patient and out-patient sampling, and year of sampling. Other research have found that residents of LTCF show high AMR and often suggest that LTCF treatment guidelines should be more in line with hospital treatment guidelines rather than general public health treatment guidelines (Rivera-Izquierdo et al., 2020).

The statistically significant higher AMR resistance rates in LTCF was found for the following antibiotics: ciprofloxacin (*E.coli, P.mirabilis* and *P.aeruginosa)*,nitrofurantoin (*E.coli)*, ceftriaxone (*E.coli)*, gentamicin (*P.mirabilis)*, fosfomycin (*P.mirabilis),* amoxicillin/clavulanic acid (*E.coli),* co-trimoxazole (*E.coli, P.mirabilis*). Ciprofloxacin, fosfomycin and ceftriaxone are listed as Highest priority critically important antimicrobials (HPCIA) in the 2024 WHO list of Medically Important Antimicrobials(Volkov, 2024). Antibiotic classification is based on the agents medical importance for treating serious diseases and the potential of AMR transmission to humans from non-human sectors. This list is intended to limit the use of HPCIA across the human and animal sector. Higher resistance of HPCIA in the LTCF cohort highlights the importance that the results of this study indicates that treatment guidelines tailored for LTCF is warranted to assist in protecting the effectivity of HPCIA.

The trend analysis for resistance rates in LTCF and community samples showed statistically significant increases in AMR over the study period. This is likely to lead to more treatment failures and limit the options healthcare professionals have for effective antibiotics and an impact on treatment practices (Laxminarayan et al., 2013). For Fosfomycin, resistance amongst *E.coli* (the commonest isolate) climbed steady during the study period (LTCF: 3.74% to 6.18%; Community: 2.75% to 3.74%) and we report higher rates than other recent South African studies which report a resistance rate of 2.2% from the Western Cape and 2% in Johannesburg (Mosime et al., 2022; Mothibi et al., 2020). Furthermore, the striking increase and current high rate of Fosfomycin resistance in isolates of K pneumoniae, P mirabilis and P aeruginosa, is likely to be of particular clinical importance. The trend analysis did not show a big difference in resistance patterns when comparing the study cohorts, but it did highlight the need for proper AMR surveillance to pick up changes in resistance such as Fosfomycin's change highlighted in this study

Similarly, resistance of *E.coli* isolates to ceftriaxone also rose (LTCF: 17.64% to 18.90%; Community: 13.32% to 17.6%). The increase in resistance is highlighted by the fact that 14.71% of total *E.coli* isolates tested positive for extended-spectrum beta-lactamase (ESBL) enzyme which is often indicative of poor treatment outcomes (Fourie J L et al., 2021).

4.2 Strengths and weaknesses

Strengths of this study include the large sample size that was used and the care that was taken to identify samples originating from long-term care facilities. An important limitation is that data from only one laboratory, which mainly serves the private sector, was used for this study. Thus, these findings may not be reflected in public sector providers with different prescribing and antimicrobial stewardship practices. The effect of the change in use of interpretive guidelines from CLSI to EUCAST during the study period is unclear; although EUCAST was utilised for the majority of the study period, reducing the risk associated with guideline change, some caution in interpreting trends the 2018 data is required. Finally, it was not possible to use clinical data about some possible confounders including frailty status, co-morbidities, previous hospitalisation, long term catheterisation, and incontinence, which are likely

to be more common in the LTCF group, possibly explaining some of the observed difference.

4.3 Implications for policy, practice and research

Despite the limitations outlined above, our findings would support other authors who, noting higher rates of AMR in LTCF-acquired infections, have proposed that LTCF-specific treatment guidelines may be needed(Rivera-Izquierdo et al., 2020). The significant increase in resistance amongst urinary pathogens, particularly Fosfomycin, is concerning and suggests that more sophisticated surveillance may be needed both in LTCF and community settings. MDR Gram negative organisms and Enterobacteriaceae is a growing concern due to the organisms ability to develop new types of resistance mechanisms (Šuto et al., 2022). *K.pneumoniae* is a species of significance due to attributes increasing the organisms pathogenicity and making it more difficult to manage and its role as a causal agent for UTIs in catheterised patients (Ameshe et al., 2022; Šuto et al., 2022). Most urine samples in this research were unclassified in terms of source, therefore it was not possible to do sub-analysis based on if a participant was catheterised. Further research is necessary to better understand different resistance mechanisms associated with *K.pneumoniae* and the impact of patient health factors such as catheterisation on AMR in the LTCF cohort vs the community cohort.

At present, there is limited clinical guidance in South Africa related to diagnosis and treatment of UTI in older people. Our study suggests that such guidance might be helpful and that specific guidance for LTCF-dwelling individuals may be needed. Appropriate antimicrobial stewardship needs to cover diagnostic approach (including distinguishing UTI from asymptomatic bacteriuria, which may not require treatment (Keuler et al., 2022).

Future research should focus on using more detailed clinical data to understand the factors which may be associated with the observed differences, and on interventions to improve antimicrobial stewardship in long-term care facilities. Extending our analyses to other types of sample and to providers which work in the public sector would provide a more detailed picture.

5. Conclusion

Escherichia coli and *Proteus mirabilis* produced the majority of significant p-values from the χ^2 analysis as well as the logistic regression. These microbes made up 60,04% of the dataset used for this study. The majority of the dataset therefore indicates that residential environment does play a role in AMR and that samples which originate from LTCF-dwelling older people often have higher *in vitro* resistance. Trend analysis in this study also showed statistically significant increase in resistance over time which is seen in both the LTCF and community-dwelling cohort with a majority of higher *in vitro* resistance rates in LTCF samples. The impact of a patient's residential environment should also be taken into account when treating a patient and might assist in better curbing the resistance health crisis.

This highlights the need for treatment guidelines specific for residents of a LTCF. Improved surveillance of resistance patterns can assist healthcare professionals to make better informed decisions regarding their antibiotic prescribing practices

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7. Declaration of Competing Interest

None declared.

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CHAPTER 4 PROTOCOL

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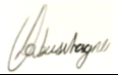
DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: Msc (Med) in Clinical Pharmacy						
PART-TIME OR FULL-TIME: Part-time			Sex:	F	X	M
FIRST REGISTERED FOR THIS DEGREE: 2022	TERM: First	YEAR: 2023				
DEPARTMENT: Department of Pharmacy and Pharmacology						
TITLE OF PROPOSED RESEARCH: **Antibacterial resistance patterns found in urine samples obtained from the elderly in Gauteng**						
CANDIDATE'S SIGNATURE: 		DATE: 14 July 2023				
SUPERVISOR 1 (NAME & SURNAME): Dr Stephanie Leigh de Rapper		50% Supervision				
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Introduction:

The health sector in South Africa is confronted with noteworthy obstacles caused by the combined effects of an aging population and a rising level of antimicrobial resistance. The elderly of our population are a vulnerable population group where their difficult health profiles often leads to misdiagnosis or inappropriate antibiotics being given. Therefore, it is imperative to obtain more accurate data on antimicrobial resistance patterns in long-term care facilities in South Africa. This information will help to direct the appropriate use of antibiotics and serve as a foundation for creating policies regarding infection prevention/control and diagnostic stewardship

Aims:

To describe antibiotic resistance patterns in microbiological samples from older people (aged >=60) and compare resistance patterns in samples from community dwelling and long term care facility (LTCF) dwelling older people.

Methodology:

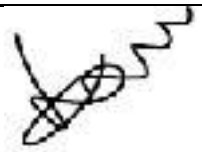
The study will collect computerised microbiology laboratory records of samples analysed by Ampath. Statistical analysis will be performed on the collected data to compare on a sample level the resistance profile of LTCF residents to community dwelling residents. The resistance patterns will be described utilising descriptive statistics. Chi Squared analysis will be performed on the data to see if there is a statistical difference between samples from LTCF residents and community dwelling residents.

Expected Outcomes:

The expected outcomes of this study are to emphasize the need for surveillance of antibiotic use and resistance to be improved in South Africa. The study will show the importance of including LTCF when working on national/ provincial antibiotic policies. The study will show medical practitioners who service LTFC what the resistance profile is for the area. This will hopefully assist them when possibly adjusting prescription habits.

WITS ETHICS NOT REQUIRED:	Yes	No	
WITS ETHICS PENDING:	Yes	No	IF Y SUPPLY ETHICS
WITS ETHICS APPROVED:	Yes	No	CLEARANCE CERTIFICATE AS
(circle appropriate symbol)*			ATTACHMENT AND INCLUDE
			ETHICS NUMBER HERE:

***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**

As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.		
SIGNATURE OF SUPERVISOR/S:		
PROTOCOL ACCEPTED BY HEAD OF DEPARTMENT/RESEARCH COORDINATOR		14 July 2023
SIGNATURE PG OFFICE STAFF ……..	REGISTERED YES….. NO…..	STAMP

11 March 2019/MP

1. Introduction

The emergence of antimicrobial resistance (AMR) has gained traction as a global health concern (Eleraky et al., 2020).This concern has also impacted South Africa where an increase in antibiotic use and antibiotic resistance has been identified in both the private and public sector (Manderson, 2020). The inappropriate and excessive use of antibiotics are one of the key driving forces behind the development and spread of AMR (Hansen et al., 2020).

A report published by the World Health Organisation (WHO) in October 2022 stated that compared to the past, the pace of population ageing has accelerated significantly (WHO, 2022). As of 2020, the number of individuals aged 60 years and above surpassed that of children under the age of 5 (WHO, 2022). South Africa is also experiencing the demographic shift reported by the WHO. According to a report from 2019, the elderly population (aged 60 years or older) constitutes 8.1% of South Africa's estimated population of 56.5 million(Stats SA, 2019). Elderly individuals are a susceptible population that is at a higher risk of infection due to advancing age and underlying health conditions (co-morbidities) that compromise their immune system and therefore their ability to combat infections (Biguenet et al., 2023). The elderly often presents with complex health statuses and minor ailments, which if not properly managed, can lead to significant deterioration of their physical condition (Leihof et al., 2021).

1.1 Antimicrobial resistance amongst the elderly

A long-term care facility (LTCF) is a specialised centre that offers residents a wide range of professional services to meet their medical and personal needs. These services include accommodation, rehabilitation, and restoration (Kalideen et al., 2022). A community dwelling elderly is defined as a person who lives outside of nursing homes/ LTCF (Chi et al., 2019).

Antibiotic overprescribing in long-term care facilities (LTCFs) is a global problem, often due to the complexity of diagnostic and treatment issues (Biguenet et al., 2023). In 2019, a study in Australia investigated the socio-demographic and health service factors associated with dispensing antibiotics to the elderly and found that the highest dispensing occurred among those residing in aged care facilities (Chen et al., 2019). The residents of LTCFs are often not only considered to be the "oldest of the old," but they are also frequently the "most frail" among the elderly population (Kalideen et al., 2022).

According to literature (Thornley et al., 2019), the diagnostic and treatment issues most relevant to residents in LTCF include;

- Elderly individuals who are frail frequently display non-specific symptoms which could be wrongly associated with infection.
- Day-to-day fluctuation in clinical presentation, due to co-morbid conditions such as dementia, of residents increase the difficulty of identifying infection.
- The presence of antibiotic resistant bacteria in care home settings can be attributed to the influx of residents who have been colonized with such organisms while receiving treatment in a hospital setting (Health Protection Scotland, 2011),
- Residents of LTCF often life in very close proximity which increases the difficulty of preventing the spread of infection (Arendse et al., 2022; Huang et al., 2023)

Several international studies have been conducted to investigate the presence of AMR in the elderly population (Pereira et al., 2016; Rivera-Izquierdo et al., 2020). Recent studies have shown high Gram-negative AMR in LTCFs residents as high as 20-30% (Jump et al., 2017). A study conducted in Taiwan investigated the rates of (MRSA) from LTCFs and hospitals; in Changhua the MRSA rate was found to be higher than the rate found in hospitals(Hsu et al., 2021). In a Spanish case series study, which looked at early diagnosis of AMR infections through anal exudates of LTCF residents found that the prevalence of multiple drug resistant organism (MDRO) colonization was 34.5%, and alarmingly, 70% of these cases had not been previously identified in the clinical records (Rivera-Izquierdo et al., 2020). Limited information is available in South Africa regarding the prevalence of infection and AMR in LTCFs.

1.2 Urinary tract infection (UTI) antimicrobial resistance amongst the elderly

A substantial portion of the population is influenced by UTIs, but generally UTIs have favourable outcomes. UTIs mostly affect women, but its prevalence increases with age in men (Myoung et al., 2021). Identifying cases of UTI in elderly can be difficult, because the elderly often presents with atypical signs and symptoms of infection (Shallcross et al., 2020). Elderly inflicted with UTI more often result in UTI-induced sepsis than in the general population (Myoung et al., 2021). UTIs in the elderly are one of the leading causes of complications such as bacteraemia, need for hospitalisation, or even death (Zeng et al., 2020).

In Scotland, the prevalence of infection in LTCFs, with urinary tract infections (UTI) and respiratory tract infections (RTI) the most common, was found to be 9.3%, which is higher than the figures reported in some European countries such as Italy and Norway (Health Protection Scotland, 2011). Infections of the urinary tract were identified as one of the most common infections in elderly (Brown et al., 2019; Cherubini et al., 2022). In 2023 a study conducted in France compared antibiotic resistance found in urine samples from three healthcare settings namely LTCF, community and hospital. They found that for certain bacteria the resistance found in LTCF were similar to the resistance found in hospitals Antibiotic resistance rate for *E. coli* in nursing homes was close to that of the community setting (Biguenet et al., 2023).

Antibiotic resistance poses a big threat to food security and healthcare professionals' ability to treat infections in South Africa (Sekyere, 2016). Antibiotic stewardship programs are essential to ensure that antibiotic use is appropriate and to limit excessive use. Countries such as the Netherlands and the United States has already demonstrated that antibiotic stewardship programs can reduce AMR within LTCF (Jump et al., 2017; Eikelenboom-Boskamp et al., 2019). The lack of evidence regarding AMR within LTCF in South Africa hampers the possibility of effective policy development and implementation. This study will aim to fill the gap regarding AMR research in the elderly in not only LTCF but a community setting as well and hopefully catalyse the process of policy development for LTCFs. Two studies investigating community acquired urinary tract infections illustrates this, as the prevalence of *E. coli* in Gauteng was 75-95% but for Bloemfontein the *E. coli* prevalence was reported as 57.6% (Lewis et al., 2013; Fourie et al., 2021).

1.3 Problem statement

The lack of a proper surveillance system in key areas, such as LTCFs, hampers efforts to understand the extent of the problem related to antibiotic use and resistance (Ekwanzala et al., 2018; Ramsamy et al., 2018). With proper surveillance, the currently used antibiotics for empiric treatment can be critically evaluated and possibly adjusted. Surveillance per area is critical because pathogens and resistance patterns differ per area and cannot be generalised. Despite the importance of LTCFs for elderly populations in Africa, there is a significant gap in published literature on the standards and quality of care for elderly residents in these facilities. This is concerning given that in South Africa alone, there are approximately 1150 public and 1000 private residential LTCFs for the elderly (Arendse et al., 2022).

Overall, addressing the problem of AMR in South African LTCFs will require a concerted effort from healthcare providers, policymakers, and the public to implement effective infection control and antimicrobial stewardship measures. This study will provide information highlighting the need for proper surveillance of AMR. The results will hopefully spark the conversation of sustainable change in antibiotic stewardship programs for the elderly in the context of an ageing population.

2. Aims and Objectives

The aim of this study is to investigate and compare the recent patterns of antimicrobial susceptibility of urine samples amongst older people (aged >=60) living in LTCFs and community- dwellings in Gauteng, South Africa. Community dwellings refer to elderly who life in a normal residential setting where there is normally no in-house professional medical care available such as in LTCFs. The aim will be achieved by means of the following objectives;

- To identify the antibiotic resistance patterns found in urine samples from elderly participants living in LTCF in Gauteng
- To identify the antibiotic resistance patterns found in urine samples from community dwelling elderly participants living in Gauteng
- To assess and compare the antibiotic resistance patterns found in urine samples from participants living in LTCF and community dwellings in Gauteng

The following hypothesis will be tested:

H_0: The antibiotic resistance patterns found in isolates from LTCF-dwelling and community-dwelling older people does not differ

H_A: The proportion of positive bacterial isolates from urinary specimens that show in vitro resistance to antibiotics is significantly greater in isolates from long-term care facilities dwelling compared with community-dwelling older people (aged >=60 years)

3. Methods

A quantitative research approach will be utilised to gather and analyse microbiological data from Ampath. Quantitative data is data with a numerical nature or which can be converted into numbers (Sheard, 2018). Quantitative data is more suitable for statistical analysis when compared to qualitative data. This is useful to uncover patterns and identify correlations hence suitable for this study.

3.1 Study design and instrumentation

The study design is a retrospective epidemiological observational study extracting and analysing anonymised data which is stored routinely in computerised microbiology laboratory records of Ampath. This design is appropriate for the quantitative big data sets that will be collected for this study.

Ampath is one of the largest pathology laboratories in South Africa. Their capacity ensures the possibility of collecting large amounts of data, making them the ideal collaborator for this study.

3.2 Study site

The laboratory records of clinical microbiology tests conducted on bacterial isolates obtained from long-term care facilities and community sites located in Gauteng Province, South Africa, and forwarded to Ampath Laboratories for examination from January 2018 to September 2023, will be utilized. Community sites refer to any location where a community dwelling elder can have urine samples sent for microbiological analysis. The list of current LTCFs in Gauteng is derived from lists published by the Department of Social Development, supplemented by online directories and is included in Appendix A.

3.3 Study population and sampling

A study population represents the target population from which the study sample is drawn and is depends directly upon the study objectives and questions addressed by the research (DeRenzo et al., 2020) The study population being used in this research is represented by participant urine samples sent for microbiological testing.

3.3.1 Inclusion and Exclusion criteria

Inclusion criteria:

- Samples obtained from participants aged >= 60 years at the time that the sample was sent for analysis.
- Samples with clinical microbiology results stored on Ampath's computer systems.
- Samples obtained within the period of January 2018 to September 2023.
- .

Exclusion criteria:

- Samples obtained from participants aged < 60 years at the time their sample was sent for analysis by Ampath
- Any samples where non-bacteria were cultured.
- Repeat samples from the same participant and sample site within a 12-week period.

3.3.2 Sample size calculation and sampling method

The sample size calculation was done utilising Stata: Release 18 (StataCorp, 2023). With a 95% confidence interval, an 80% power and assuming a baseline resistance incidence in LTCF to be 40% and in the community to be 35%, a sample size of 1468 is needed per group if sample sizes for the two groups are equal. Records from January 2018 up until September 2023 will be utilised with an estimate of 15 000 records per year. The study uses convenience sampling for participant selection. There is no sampling pattern involved in convenience sampling (Galloway, 2005).

3.3.3 Population selection

Participant selection will take place by searching Ampath's database for microbiological reports that meet the inclusion and exclusion criteria of the study. All data from Ampath will be anonymised and no personal data which can be linked to the participant such as date of birth will be collected. There is therefore no direct participation of participants in this study and no participant informed consent will be utilised for this study.

To maintain the independence of samples in data analysis, any repeated isolates obtained from the same participant and the same sample site (urine) within a 12-week period will be excluded. This approach aims to avoid potential biases and prevent the results to be skewed towards more resistance by including repeat samples from more resistant organisms. Consequently, this will enhance the robustness of the data analysis and improve the accuracy of the results obtained.

3.4 Study procedure

3.4.1 Data collection

The following data will be extracted from Ampath's clinical database, and stored in a dedicated location within Ampath's computer network for cleaning and anonymisation with the assistance of a dedicated, pre-identified Ampath pathologist:

- Participant details including age and gender
- Clinical facility location (from where the sample was sent)
- Sample requisition number
- Date of sampling
- Sample site or type (e.g. urine).
- Microscopy and culture results
- Antimicrobial sensitivities for positive culture results
- Doctor copy number

The above-mentioned participant identifiable variables will be utilised to ensure that records are matched to specific patients and duplicate records or repeat samples be identified and removed. The clinical facility location, doctor copy number and residential address of the participant will be used to formulate a narrative for the participant and identify if the participant lives in a LTCF. The variables which will be utilised for data analysis in this study is the participant age, gender, date of sampling, microscopy and culture results and antimicrobial sensitivities for positive culture results.

3.4.2 Data classification:

Data will be classified according to the setting in which the samples are collected. A list of current long term care facilities (Appendix A) within Gauteng Province will be sent to Ampath to form a basis to classify the data point as community dwelling or LTCF dwelling. The microbiological reports extracted from Ampath will list the name of the setting where the sample was obtained. Participants will be classified as:

- Community-dwelling (living in their own home as their usual address), or
- Long-term care facility (LTCF) -dwelling (living in a LTCF – retirement village, frail care, etc as their usual address).

3.4.3 Data cleaning and anonymisation:

This will be conducted within Ampath's computer network using their network program (so that no identifiable data leaves the network). Data cleaning and anonymisation will be done by utilising Microsoft Access. Data cleaning and anonymisation will be done under the direct supervision of a dedicated, pre-identified, Ampath pathologist to ensure that no private or confidential information leaves the network.

3.5 Data processing methods

Secondary data analysis is becoming more popular as it is more cost effective to perform. It is however important to keep in mind that the data collection was not designed to answer a specific research question. A common problem with secondary analysis is the presence of missing data which can bias the results (Alexander et al., 2021; Cole and Trinh, 2017).

To ensure that this study does not bias the data and that the data collected will be suitable for the study objectives, records containing missing data pertaining to the microbiological test result or living environment will be excluded in this study. After data extraction and anonymisation, the data analysis will be performed using Excel. For ease of data analysis, intermediate antibiotic resistance results will be classified with sensitive results as the bacteria is still sensitive to such an agent but only at a higher dose. Appendix B – Data analysis review tool shows how the data will be summarised for analysis.

3.6 Statistical analysis

Statistical analysis will be performed in Stata release 18 (StataCorp, 2023). Table summarises the statistical analysis plan that will be used to measure the objectives of the research.

Table 1: Statistical methods that will be used per objectives of this research

Objective	**Variables**	**Statistical test/s**
To identify the antibiotic resistance patterns found in urine samples from elderly participants living in LTCF in Gauteng	Antibiotic resistance results	Incidence of positive resistance results and specific organisms cultured (as a proportion of total and positive resistance results) will be presented as

		descriptive statistics for LTCF dwelling and community dwelling participants. This will be done for every clinically important bacterium antibiotic susceptibility result.
To identify the antibiotic resistance patterns found in urine samples from community dwelling elderly participants living Gauteng	Antibiotic resistance results	Incidence of positive resistance results and specific organisms cultured (as a proportion of total and positive resistance results) will be presented as descriptive statistics for LTCF dwelling and community dwelling participants. This will be done for every clinically important bacterium antibiotic susceptibility result.
To compare the antibiotic resistance patterns found in urine samples from participants living in LTCF and community dwellings in Gauteng	Comparison of resistance proportions between the two study groups	Chi squared analysis. A P-value of <0.05 will be seen as statistically significant.

4. Ethics

Ethics will be applied for from the Wits Human Research Ethics Committee (HREC). Confidentiality of participants will be ensured in that all data extracted from the Ampath server

will be anonymised by Ampath. Only anonymised data will be used for further analysis. No participant identifiable data such as date of birth will also be collected to ensure confidentiality.

This study will only use routine clinical data. No additional data from participants, interview or surveys will be applied, neither the collection of samples or performance of procedures on participants as part of this study. A letter of authorisation to utilise Ampath data can be found in Appendix C – Ampath Permission letter.

5. Timing

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Writing of Protocol												
Preparing ethics application												
Submit for ethics clearance												
Obtain ethics clearance												
Data extraction and anonymisation												
Data analysis of data set												
Write-up												

6. Funding

Funding applications will be made to the National Research Fund. Any additional funding will be obtained through the research supervisors research funds including RINC.

7. Budget

The study is mainly focussed on data analysis and will therefore require minimum funds.

Budget Item	**2023**
Printing and stationary costs	R600
Cell phone airtime costs	R200
Traveling costs	R400
Total study costs	R1200

8. Project limitations

This study has limitations which can be addressed by possible future research. The limitations include:

- Only microbiological data available on Ampath's system is being utilised. Microbiological data from other pathology labs such as National Health Laboratory Service (NHLS), Pathcare or Lancet. Therefore, only a subset of data from the population is used.
- AMR is a complex multifaceted health problem which is influenced by many confounding variables. In this study only microbiological data is used and no clinical data or background from the participant is used.
- Antifungal resistance is a growing health concern, especially in the elderly community that form part of this study's population, but is not investigated in this study.
- Infections where the medical practitioners do not send a sample for culture will not be picked up in this study.
- This study will show the resistance profile of bacterial isolates but will not look at which antibiotic was prescribed to the participant and if the antibiotic is appropriate.
- Accuracy of data captured on Ampath system.
- The period of data collected falls over the COVID-19 period which can affect susceptibility results over that period.

9. Dissemination and translation of research

This research will be disseminated by means of published research articles in reputable peer-reviewed journals, as well as presenting findings at scientific conferences. Translation of research goes beyond dissemination by actively facilitating the integration of research outcomes into real-world settings. This research will be presented to policy makers and laboratories in the form of research summaries, and toolkits that enable the effective application of research findings in different contexts.

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Appendix A - LTCF

Name of Home	City/Town	Address
Abbey Cross Lodge	Randburg	442 Felstead Rd, Northriding, Roodepoort, 2169
AD Care Frail care clinic	Waterkloof Ridge	173 Regulus St, Waterkloof, Pretoria, 0181
AGS Tehuis	Rietfontein	695 Frederika St, Rietfontein, Pretoria, 0084
AGS Ouetehuis	Centurion	26 Village Street, Irene, Centurion, 0062
AGS Tehuis Villieria	Villieria	1085 Hertzog St, Villieria, Pretoria, 0186
Aldem Healthcare De Groenkloof	Groenkloof	234 Schroeder Street, Groenkloof Pretoria, 0027
Alden Healthcare The Retreat		The Retreat Retirement Village, 31 Top Flight Avenue, Hazeldean Pretoria, 0084
Andries Snyman Rusoord Vir Bejaardes	Eersterust	236 Elsrivier St, Eersterust, Pretoria, 0022
Arbor Village	Bedfordview	0A Smith Rd, Bedfordview, Germiston, 2008
Blymoedig Kliniek	Pretoria	Plot 42. Nieshout Road Kameeldrift East Pretoria
Bouganvilla Retirement Village	Montana	Bougainvillea Rylaan 1556, Montana Tuine, 0182, Pretoria
Bousfield Lodge Retirement Village	Gezina	Malan St, Prinshof 349-Jr, Pretoria, 0084
Bronberg Retirement Village	Olympus	47 Midas Avenue, Olympus Drive

Care in Midstream	Midstream	Care in Midstream, 1 Madeleine Street, Retire@Midstream Building, Midstream
Caro House Old age Home	Northcliff	24 Lawley Ave, Waterval Estate, Randburg, 2195
Deansgate Retirement Village	Craighall park	21 Herpo Rd, Craighall Park, Randburg, 2196
De Meerpal	Alkantrand	689 Stellenberg Rd, Pretoria
Deo Gratia	Garsfontein	257 Hilda Botha St, Garsfontein, Pretoria, 0042
Deutsches Alterheim	Groenkloof	Napier Rd, Richmond, Johannesburg, 2092
Die Kronedal	Arcadia	227 Wessels St, Arcadia, Pretoria, 0007
Ebenhaeser	Kilnerpark	211 Anna Wilson St, Kilner Park, Pretoria, 0186
Eden Care Centres	Villieria	1085 Hertzog St, Waverley, Pretoria, 0186
Ekklesia park	Randburg	2 Park Ln, Blairgowrie, Randburg, 2194
Ons tuis Emily Hobhouse	Pretoria	Malherbestraat 55, Capital Park, Pretoria
Ons tuis Machteld Postmus	Equestria	Mackenziestraat 225, Brooklyn, Pretoria
Ons tuis Van Rensburg	Danville	Delaneystraat 69, Danville, Pretoria 0183
Seniorstuis dienssentrum	Riviera	Ingang Parkerstraat, Riviera, Pretoria
Ons tuis Riviera	Riviera	Soutpansbergweg 180, Riviera, Pretoria 0084

Ons tuis Louis Trichard	Danville	Danweg 127, Danville, Pretoria
Evergreen Broadacres Retirement Village	Fourways	43 Frederick Rd, Broadacres Park, Johannesburg, 2194
Faerie Glen Renaissance	Faerie Glen	45 Haymeadow Cres, Faerie Glen, Pretoria, 0081
Fairland Retirement Village	Fairland	Fairland Village, 150 Smit St, Fairland, Johannesburg, 1925
Featherwood Retirement Village	Pretorius Park	131 Mat Ave, Pretoriuspark, Pretoria, 0042
Fleurenville Retirement Village Montana	Montana	470 Jan Bantjies Rd, Montana, Pretoria, 0151
Golden Harvest	Randburg	C/O 5th Street and Fourth Road,
Glenhaven	Garsfontein	282 Annette Van Zyl St, Garsfontein, Pretoria, 0081
Haven Village	Garsfontein	269 Emmie Hartmann St, Garsfontein, Pretoria, 0081
Harmonie Hof	Sunnyside	Steve Biko Straat 129, Sunnyside
Harmonie Oord	Sunnyside	Steve Biko Straat 125,
Henley River Care Centre	Henley on Klip	109 Ewelme rd, Corner Wargrave South, Henley on Klip, 1962
Hermon Sentrum	Wonderboom	469 Generaal De Wet Street
Highveld Gardens Retirement Home	Johannesburg	Halfway House, 212 Old Rd, Halfway Gardens, Midrand, 1680
Holy Cross Home	Hercules	885 Mosesh St, Claremont, Pretoria, 0055
Hospicare	Roodepoort	104 Umgeni Rd, Wilro Park, Roodepoort, 1724
Huis Eljorie	Kilner Park	28 Owen Ave, Kilner Park, Pretoria, 0186

Huis Harold Abrahamse	Groenkloof	237 Schroder St, Groenkloof, Pretoria, 0027
Huis Annezel	East Lynne	64 Troupant Ave, East Lynne, Pretoria, 0186
Huis H J Piek	Groenkloof	153 Middle St, Nieuw Muckleneuk, Pretoria, 0181
Huis Herfsblaar	Queenswood	1244 Webb Rd, Queenswood, Pretoria, 0186
Huis Lodewyk Spies	Eersterus	271 Soutrivier Avenue, Eersterus, 0022
Huis Lucas	W/boom Ldbou	6 Chervil Ave, Annlin, Pretoria, 0066
Huis Protea	Germiston	Churchill Ave, Primrose, Germiston, 1401
Huis Vergenoeg	Villeria	entrance 3, 830 33rd Ave, Villieria, Pretoria, 0186
Jafta Jewish Home	B/ Muckleneuk	42 Mackie St, Bailey`s Muckleneuk, Pretoria, 0181
Jakaranda Haven	Groenkloof	44 Charles Bramley Street Bailey's Muckleneuk Pretoria
Junes Haven Frail Care	Parktown West	28 Seymour Avenue, Parktown, 2193, Johannesburg, 2937
Karmel	Sunnyside	40 Troye St, Sunnyside, Pretoria, 0002
Kensington Gardens	Kensington	75 11th Ave, Kensington, Johannesburg, 2094
Kingswood Retirement village	Newlands	317 Gay St, Newlands, Pretoria, 0181
Lonehill Manor Retirement Village	Sandton	76 Concourse Cres, Lone Hill, Johannesburg, 2055

Mamelodi O. A Home	Mamelodi West	117 Tshama-Hansi St, Mamelodi, Pretoria, 0122
Masonic Haven	The Willows	58 Jukskei Ave, Die Wilgers, Pretoria, 0184
Maxhaven Retirement village	Cresta	15 Danie St, Cresta, Johannesburg, 2194
Machteld Postumus	Pretoria	Mackenzie Street, Brooklyn, Pretoria, 0181
Medifrail Centurion	Lyttelton	110 Napier Rd, Lyttelton, Centurion, 0157
Medifrail Equestria	Equestria	977 Cura Ave, Equestria, Pretoria, 0181
Medifrail Hennops River	Hennops river	Plot 119, R511, Centurion
Medifrail Olive Crescent	Olympus	Olive Ln, Olympus AH, Pretoria, 0081
Mirtehof	Daspoort	733 Van Riebeeck St, Daspoort, Pretoria, 0001
Montana Renaissance	Montana	1057 Braam Pretorius St, Montana Park, Pretoria, 0182
Montana Retirement Village	Montana	900 Klippan St, Montana, Pretoria, 0151
Mooigelee Sorgeenheid	Faerie Glen	588 Graaff Reinet St, Faerie Glen, Pretoria, 0081
Mothwa Haven	Les Marais	353 Booysen St, Eloffsdal, Pretoria, 0084
Nazareth House	Waterkloof	290 Queen Wilhelmina Dr, Waterkloof, Pretoria, 0181
Nazareth House	Johannesburg	Webb St, Yeoville, Johannesburg, 2198
Nebohof	Sunnyside	Sunnyside, Pretoria, 0002

Nieuwoudtshof Tehuis	Waverley	1393 Dunwoodie Ave, Waverley, Pretoria, 0135
Oostvallei Retirement Village	Garsfontein	657 Coley St, Garsfontein, Pretoria, 0042
Palms Renaissance	Silverton	684 Pretoria Rd, Silverton, Pretoria, 0184
Prestigepark Retirement Village	Pretoria	314 Scheiding St, Pretoria Central, Pretoria, 0002
Primrose Place Frial Care	Northcliff	Elm Park Retirement village, 1 Suzanne Cres, Northcliff, Johannesburg, 2195
Princess Christian Home	Groenkloof	Middel St, Nieuw Muckleneuk, Pretoria, 0181
Protea Retirement Village	The Willows	105 Swaardlelie Ave, Die Wilgers, Pretoria, 0184
Rand Aid, Thornhull Manor Retirement village	Modderfontein	158 Westlake Drive, Lakeside Village, Johannesburg Rd, Modderfontein, 1645
Resthill Memory Care	Centurion	Plot 105 Pretorius St, Laezonia AH, Centurion, 0026
Riversands Retirement Village	Heidelberg	Corner of Bosbok and, Leeu St, Jordaanpark, Heidelberg - GP, 1441
Rosendal Retirement	Arcadia	585 Pretorius St, Arcadia, Pretoria, 0083
Ruimsig Retirement Village	Waterkloof	9 Flora Haase Rd, Amorosa, Roodepoort, 1723
SAVF Huis Silwersig	Silverton	513 Jasmyn Ave, Silverton, Pretoria, 0127
SAVF M. Ackerman	Pretoria West	464 Vom Hagen St, Pretoria West, Pretoria, 0183

Sederberg Retirement Village	Pretoria	380 Sisulu St, Pretoria Central, Pretoria, 0002
Selrose Park Retirement Village	Equestria	4 Griffiths Ave, Equestria, Pretoria, 0184
Serene Park Retirement Centre	Garsfontein	245 Johnny Claassens St, Garsfontein, Pretoria, 0081
Silver Stream Retirement Village	Malanhof	9 Heather St, Malanshof, Randburg, 2194
Sonnheim Retirement Centre	Arcadia	268 Hamilton St, Arcadia, Pretoria, 0007
Susan Strijdom	Sunnyside	116 Doreen St, Colbyn, Pretoria, 0083
The Golden Years	Jukskei park	61 Robyn St, Julskeipark, Randburg, 2191
The Retreat at Hazeldean	Hazeldean	31 Top Flight Ave, Hazeldean, Tyger Valley, 0084
The Whole of the Moon	Benoni	91 Rennie Rd, Benoni North AH, Benoni, 1509
Trans-50 Jakaranda Park Retirement Village	Rietfontein	646 23rd Avenue, Rietfontein, Pretoria
Tree of Life Care	Eldoraigne	58 Hyde Ave, Eldoraigne, Centurion, 0157
Twee Riviere Retirement Village	Montana	Twee Riviere Retirement Village, Breed Street, Montana, Pretoria, 0159
Uncle Ben's Den	Hermanstad	887 Botha St, Daspoort, Pretoria, 0019
Van Rensburg Monument	Pretoria	69 Delaney Street
Vergelegen Retirement Village	Equestria	90 Vergelegen Avenue,. Equestria,. Pretoria East.

Waterkloof Marina Retirement Estate	Waterkloof Ridge	296 Orion Ave, Waterkloof Ridge, Pretoria, 0181
Westview Lodge	Sandton	40 Westview Dr, Bryanston, Randburg, 2060
Wilgers Retirement Village	The Willows	Wilgers Retirement Village, 120 Trollope Rd, Die Wilgers, Pretoria, 0041
Willow Haven Retirement Village	The Willows	139 Harte St, The Willows, Pretoria, 0184
Willow Village Retirement Home	The Willows	321 Spitskop Rd, Die Wilgers, Pretoria, 0184
Willowbrook Retirement Village	Sandton	134 Willowbrook Pl, Sandown, Sandton, 2196
Witpoortjie Retirement village	Roodepoort	69 Dromedaris St, Witpoortjie, Roodepoort, 1724
Zambesi Retirement Village	Montana	531 Sefako Makgatho Dr, Montana, Pretoria, 0151

Appendix B – Data analysis review tool

LTCF					Community				
Age: 60-64 *	Organism A	**Antibiotic name**	**Susceptible**	**Resistant**	Age: 60-64	Organism A	**Antibiotic name**	**Susceptible**	**Resistant**
		Antibiotic A					Antibiotic A		
		Antibiotic B					Antibiotic B		
		Antibiotic C					Antibiotic C		
		Antibiotic D					Antibiotic D		
Age: 65-69	Organism A	**Antibiotic name**	**Susceptible**	**Resistant**	Age: 65-69	Organism A	**Antibiotic name**	**Susceptible**	**Resistant**
		Antibiotic A					Antibiotic A		
		Antibiotic B					Antibiotic B		
		Antibiotic C					Antibiotic C		
		Antibiotic D					Antibiotic D		
		Antibiotic A					Antibiotic A		
		Antibiotic B					Antibiotic B		
		Antibiotic C					Antibiotic C		
		Antibiotic D					Antibiotic D		

*This review tool will be utilised for all data from participants 60 years and older. The ages might be grouped utilising a 5 year interval as displayed above.

Appendix C – Ampath Permission letter

24 JULY 2023

UNIVERSITY OF THE WITWATERSRAND

RESEARCH OFFICE SECRETARIAT

Your reference: Protocol Reference No: MED 23-06-154

For Attention:

Ms Mapula Ramaila

Administrative Officer

Human Research Ethics Committee (Medical)

Copy to: Dr Stephanie Leigh-de Rapper

Stephanie.derapper@wits.ac.za

Dear Ms Ramaila

RE: STUDY PROPOSAL: Antibacterial resistance patterns found in urine samples obtained from the elderly in Gauteng

Principal Investigator: Mrs Olivia Labuschagne (Student number: 1118354)

('the Candidate")

The abovementioned matter kindly refers.

Our Laboratory, Drs. Du Buisson, Kramer, Swart, Bouwer Incorporated hereby grants consent that the Candidate may utilise the anonymous data of relevant patients in the possession of our laboratory for the aforesaid study.

This consent is subject:

1. To Relevant legislation including but not limited to the Protection of Personal Information Act 4 of 2013 (POPI), the National Health Act 61 of 2003 (NHA) and regulations to these Acts and specifically more so the following Regulation issued under the NHA:

REGULATIONS RELATING TO RESEARCH WITH HUMAN PARTICIPANTS

Published under Government Notice R719 in Government Gazette 38000 of 19 September 2014.

2. Thereto that no personal data of any patient or his/her relations may be used in the study and that only anonymised/de-identified patient data will be supplied by our Practice;
3. The disclaimer and indemnity signed between our Practice and the Candidate;
4. That no data extrapolated or generated from the study may be used for any commercial application;
5. That our Practice's name may only be mentioned in any internal or external communication or publication if written consent is granted thereto by our Chief Executive Officer, Dr Ebrahim Hoosien;
6. That the Candidate maintains her registration with your Institution;
7. That Ethics approval for the Study be finally granted and to remain valid and not be withdrawn by your Institution/any Ethics Committee;
8. That our Practice may withdraw this consent by written notice to your Institution and to Candidate should information come to our knowledge which may be prejudicial to our Practice's reputation;
9. Our Practice's Standard Operating Procedures;
10. That the Candidate complies with any reasonable and lawful request by our senior management;

11. That our Practice and its suppliers' intellectual property and confidential business information be respected and be honoured;

12. That the conditions referred to in your letter dated 20 July 2023 as well as the letter signed by Dr Stephanie Leigh-de Rapper on behalf of your Department of Pharmacy and Pharmacology dated 9 May 2023, attached hereto be adhered to.

We trust you find the above conditions in order and wish the Candidate success with her research.

Should you kindly wish to discuss this, kindly contact writer.

Dr. Craig Corcoran
Chief Operations Officer

CHAPTER 5 APPENDICES

5.1 Postgraduate Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

30 January 2024
Person No: 1118354
PAG

Mrs O Labuschagne
692 Conan street
Unit 43 La Residence
Moreletapark
0181
South Africa

Dear Mrs Olivia Labuschagne

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Antibacterial resistance patterns found in urine samples obtained from the elderly in Gauteng* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.2 Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Mrs Olivia Labuschagne

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230669 MED23-06-154

NAME: (Principal Investigator)	Mrs Olivia Labuschagne
DEPARTMENT:	Pharmacy and Pharmacology
DEGREE:	Master of Science in Medicine
PROJECT TITLE:	*Antibacterial resistance patterns found in urine samples obtained from the elderly in Gauteng*
DATE CONSIDERED:	30/06/2023
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - Nicoleen.Potgieter@wits.ac.za
SUPERVISOR:	Dr S. De Rapper
APPROVED BY:	Professor Paul Ruff, Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/10/2023 **EXPIRY DATE:** 25/10/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

26 - October - 2023
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES