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Colonisation with pathogenic drug-resistant bacteria and *Clostridioides difficile* among residents of residential care facilities in Cape Town, South Africa.

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Declaration

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**ABSTRACT**

**Objectives**

Residential care facilities (RCFs) act as reservoirs for multidrug-resistant organisms (MDRO). There are scarce data on colonisation with MDROs in Africa. We aimed to determine the prevalence of MDROs and *C. difficile* and risk factors for carriage amongst residents of RCFs in Cape Town, South Africa.

**Methods**

We performed a cross-sectional surveillance study at three RCFs. Chromogenic agar was used to screen skin swabs for methicillin-resistant *Staphylococcus aureus* (MRSA) and stool samples for extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E). Antigen testing and PCR was used to detect *Clostridioides difficile*. Risk factors for colonisation were determined with logistic regression.

**Results**

One hundred fifty-four residents were enrolled, providing 119 stool samples and 152 sets of skin swabs. Twenty-seven (22.7%) stool samples were positive for ESBL-E, and 13 (8.6%) residents had at least one skin swab positive for MRSA. Two (1.6%) stool samples tested positive for *C. difficile*. Poor functional status (OR 1.3 (95% CI, 1.0 – 1.6)) and incontinence (OR 2.9 (95% CI, 1.2 – 6.9)) were significant predictors for ESBL-E colonisation. There was a trend towards higher MRSA colonisation in frail care areas.

**Conclusion**

There was high prevalence of colonisation with MDROs but low *C. difficile* carriage, with implications for antibiotic prescribing and infection control practice.
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List of abbreviations

Antibiotic resistance (ABR)

Carbapenem-resistant *Enterobacterales* (CRE)

Center for Disease Control (CDC)

*Clostridioides difficile* infection (CDI)

Extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E)

Healthcare-associated infection (HAI)

Infection prevention and control (IPC)

*Klebsiella pneumoniae* carbapenemase (KPC)

Long-term care facilities (LTCFs)

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Multidrug-resistant organisms (MDRO).

Residential care facilities (RCFs)

World Health Organisation (WHO)
CHAPTER 1: LITERATURE REVIEW

Introduction

Antibiotic resistance (ABR) is a global public health crisis which threatens to undermine our ability to treat bacterial infections [1, 2]. Therapeutic options to treat these infections are becoming limited as ABR has been evolving and disseminating at rates congruent with antibiotic usage [2]. ABR carries a high mortality and if no action is taken to limit its spread, it is estimated that up to 10 million annual ABR-related deaths will occur globally by 2050 [3].

ABR is common in South African referral hospitals. Local studies have shown that up to 74% of Klebsiella pneumoniae bloodstream isolates from South African (SA) public sector hospitals are extended-spectrum beta-lactamase (ESBL) producers [4], defined as being resistant to beta-lactam antibiotics, including third-generation cephalosporins such as cefotaxime, ceftriaxone, and ceftazidime. Similarly, over half of Staphylococcus aureus bloodstream infections at Groote Schuur hospital (GSH) in Cape Town are resistant to cloxacillin [5]. Resistance of urinary Escherichia coli isolates to ciprofloxacin is increasing in SA with rates close to 20% [6].

The rise in multiresistant bacteria has necessitated a change in empiric antibiotic prescribing practices, and patients with healthcare-associated infection (HAI) are now treated with broad-spectrum second-line antibiotics such as carbapenems and vancomycin [7]. It has been shown that use of carbapenem antibiotics can lead directly to the emergence of carbapenem-resistance during therapy, [8] and there are concerns that drug pressure from widespread carbapenem use may contribute to the emerging problem of carbapenem-resistant Enterobacterales (CRE). CRE have been reported from all major public hospitals in SA.

There are no published data on the prevalence of colonisation with ABR bacteria or Clostridiodes difficile amongst residents of residential care facilities (RCFs) in South Africa, but this is needed to guide recommendations for empiric antibiotic prescribing and infection control practices in these facilities.

Mechanisms of antibiotic resistance

Excessive antibiotic consumption in human health and the environment may contribute to the emerging problem of ABR [9, 10]. Empiric antibiotic prescribing practices (particularly with broad-spectrum antibiotics) lead to an increased risk of colonisation with ABR bacteria [11].

Bacteria have a remarkable ability to respond to an array of environmental threats that may threaten their existence. It may be underappreciated that some resistance mechanisms are ecologically ancient and that multiple mechanisms including 1) alterations of target site, 2) over-expression of efflux pumps and 3) protection of target sites may be used in isolation or in combination to confer resistance[9].
ABR is linked to: 1) not utilising local antibiotic susceptibility data, 2) use of broad-spectrum antibiotics where not indicated, 3) treatment of contamination and colonisation rather than infection, 4) inappropriate surgical prophylaxis, and 5) prolonged treatment with antibiotics [7]. Higher levels of colonisation with ABR bacteria have been demonstrated in patients with a viral pneumonia who received prolonged antibiotic therapy after virus identification [11].

**Antibiotic resistance in Africa**

There is limited data on ABR in Africa and particularly Sub-Saharan Africa, with almost half of African countries reporting no ABR prevalence data. Certain factors have been highlighted by a systematic review about the flaws and inaccuracies of published data on ABR in Africa; these include 1) biased data from a limited number of countries with a strong regional preponderance, 2) questionable quality of susceptibility testing methods, 3) poor representation from rural populations and 4) lack of recent studies [12, 13].

Despite this, a high prevalence of ABR to commonly used antibiotics has been demonstrated [12, 14]. A recent systematic review by Leopold et al. demonstrated high-level resistance to ampicillin (55.6-96%) and co-trimoxazole (51.0-86.7%) in patients with a febrile illness who had a positive *Enterobacterales* isolate (source of isolate unknown) [12]. The prevalence of resistance for respiratory isolates was variable with low rates reported for *Streptococcus pneumoniae* to erythromycin (0.0-5.9%), while significant resistance to tetracycline was demonstrated for both *Haemophilus influenzae* (100%) and *S.pneumoniae* (42%) [12]. In a similar systematic review the median resistance of *S.pneumoniae* to penicillin was 25%, and 34% for *H.influenzae* to amoxicillin. Resistance of *Salmonella typhi* to ciprofloxacin was reported to be rare [14].

Communicable diseases in Africa are a major cause of death. They lead to extensive use of antibiotics with resultant ABR and its associated health and financial costs. No African country has a national surveillance system for ABR and few have national infection prevention and control (IPC) policies. Only two have implemented national action plans to combat ABR in accordance with a World Health Organisation (WHO) mandate [15].

Perhaps the greatest threat to human health is the emergence of multi-resistant Gram-negative bacteria and in particular ESBL producers and CRE; infections caused by these organisms are associated with increased mortality, longer hospital stays and excessive hospital costs [16, 17]. In a systematic review performed by Tadesse et al on ABR in Africa, high-level resistance of *E. coli* (20.0% and 19.5%) and *K. pneumoniae isolates* (34.2% and 46.7%) to 3rd generation cephalosporins (ceftriaxone and cefotaxime) was demonstrated. This is concerning as this may represent ESBL production [14].

In 2011 the emergence of CRE was confirmed for the first time in South Africa. It was also the first time *Klebsiella pneumoniae* carbapenemase (KPC) producers had been demonstrated in Africa [16]. In 2013 the Center for Disease Control (CDC) in the United States declared CRE an immediate health threat requiring urgent and aggressive action.
The major factors for acquisition of CRE are similar to those for ESBL and include antibiotic exposure, intensive care unit admission, poor functional status, prolonged hospitalisation and surgery. Residential care facilities (RCFs) are known to be reservoirs of ESBLs but may also harbour CRE as they provide ideal conditions for their emergence and dissemination [1].

**Antibiotic resistance in South Africa**

The exact burden of ABR in South Africa (SA) is unknown. This is a major concern as infections result in the greatest burden of disease is SA. Empiric antibiotic prescribing practices which are not directed by local antibiogram data are frequently employed to combat these infections and may contribute to the development of ABR [18].

In most South African hospitals (public and private sector) antibiotic management is generally unacceptable and inappropriate in terms of 1) treatment duration, 2) avoidance of de-escalation where possible and 3) use of multiple agents. Clinicians are unfamiliar with antibiotic stewardship principles and these recommendations are often ignored [1].

In a 2018 report by the National Institute for Communicable Diseases (NICD) on ABR in South African public sector hospitals (both HAI and community-acquired infections) the following alarming results were demonstrated. Among *K. pneumoniae* isolates: 36% were resistant to ciprofloxacin, 44% to piperacillin/tazobactam and 59% to gentamicin; with 65% (perhaps most alarmingly) being categorized as ESBL producers. Less than 30% of *E.coli* isolates demonstrated ESBL production. Approximately two-thirds of *S. aureus* isolates were categorised as methicillin-resistant *Staphylococcus aureus* (MRSA). Low-level resistance of *Enterococcus faecalis* and *Enterococcus faecium* to glycopeptides was demonstrated [19].

In a similar report on ABR surveillance from 4 South African private sector hospitals [20], antibiotic susceptibility testing was performed on ESKAPE (*Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterobacter cloacae and Eschericia coli*) bloodstream isolates. *K.pneumoniae* isolates demonstrated significant resistance to 3rd generation cephalosporins (55-57%) but were susceptible to carbapenems. A quarter of *S.aureus* bloodstream isolates were classified as MRSA. ESBL production in both *K.pneumoniae* and *E.coli* isolates was surprisingly lower in private compared to public sector hospitals.

Healthcare-associated infections (HAI) carry a high mortality and result in excessive healthcare expenditure and prolonged hospital stay [21]. HAI are common in long-term care facilities [22]. Allegranzi et al. demonstrated that prevalence rates of HAI in developing countries (15.5 per 100 patients) was considerably higher (3 times the level) than those reported from the US [23]. Infections that arise in residents from residential and long-term care facilities are now treated as healthcare-associated infections [7].
Residential care facilities

The world’s population is aging and it is expected that the number of people aged greater than 60 years will double by 2050; the majority of whom will reside in developing regions [24]. Residential care facilities (RCFs) are becoming major components of healthcare systems globally. In the US the number of residents in these facilities is expected to increase from 15 to 27 million by 2050[25].

Significant ambiguity exists in the literature regarding definitions of related terms such as “long term care facility” (a facility that provides room and board, as well as management of chronic medical conditions and 24-hour assistance with ADLs in patients who are physically and/or cognitively impaired) and “residential care facility” (a facility that provides room and board, housekeeping, supervision, assistance with ADLs and distributions of medications) and “nursing home” and their application in different countries. They are often used interchangeably. For example, in the United States, long term care usually occurs in residential care facilities, long-term care facilities (where nursing care is generally more intensive) and care homes. A recent international survey on the understanding of these terms demonstrated certain salient features that may be applied to characterize different facilities. These included 1) duration of stay (short versus long-term), 2) level of care required by residents with activities of daily living (ADL’s), 3) degree of skilled workers in these facilities (specialist nurses and physicians) and 4) goals in terms of improving resident functional status. Despite these suggestions many facilities have heterogenous populations requiring different levels of care who live in areas designated specifically for their needs, overlapping and confounding proposed definitions. It is important to describe details about number of residents, their functional status, availability of health staff, resources and services offered at a particular facility in addition to applying formal definitions[26].

Populations in long-term care facilities (LTCFs), and residential care facilities (RCFs) in particular, are unique in that they (1) are institutionalised, (2) have multiple exposures to antibiotics, (3) have multiple medical comorbidities, (4) frequently have indwelling devices, (5) have frequent admissions to acute care facilities, (6) have impaired mobility, and (7) altered immunity. These factors place residents of RCFs at increased risk for colonisation and infection with ABR bacteria [27]. Colonisation (defined as asymptomatic carriage) with ABR bacteria is a well-established risk factor for infection with the same strain [17, 28], particularly in immunocompromised and elderly populations [29, 30]. RCFs are increasingly recognised as reservoirs for ABRs [17, 31, 32] and colonisation with ABR bacteria has been associated with outbreaks after referral of RCF residents to acute care facilities [33].

A point prevalence study of LTCFs in Italy found that three quarters of residents were colonised with ≥ 1 resistant organism, 64% with ESBL producers and 39% with methicillin-resistant S aureus MRSA [32]. Studies from the United States have shown similarly high rates of
colonisation with ESBLs, MRSA and ciprofloxacin-resistant Gram-negative bacilli [27]. Studies in high-income settings have demonstrated MRSA prevalence rates between 16% and 50% in various RCF populations [34, 35], [36].

Additionally, residents of RCFs in high-income countries have high rates of *Clostridioides difficile* (previously *Clostridium difficile*) colonisation [37] and are susceptible to *C. difficile* infection (CDI) because of advanced age and frequent antibiotic use [38]. Colonisation with ABR organisms is also associated with prolonged hospital stay with increased hospital costs [39].

There is a large amount of variability in published ABR prevalence amongst long-term care facility residents. Estimates of extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) colonisation in European series ranged between 4% and 64% [31, 32, 40, 41], similar to reports from the US [17, 27]. The wide range in prevalence is likely due to heterogeneity in study population. For example, inconsistent definitions of ‘long-term care facility’ are applied, some of which encompass acute care step down facilities expected to have higher prevalence of multi-drug resistant organisms compared with RCFs, where residents are less sick and have less exposure to antibiotics [42-44]. ESBL-E colonisation was detected in 12% of residents (n = 119) in 3 residential aged care facilities in Australia [45]. In Belfast, Ireland, very high rates of ESBL-E colonisation (40%) were reported from 294 residents across 16 nursing homes [46].

Gram-negative bacteria have a propensity to acquire and develop antibiotic resistance [47]. These pathogens were previously considered to be nosocomial pathogens, but it is now evident that they have spread to other healthcare settings and the community. High levels of colonisation with these organisms have been demonstrated upon admission to acute care hospitals with the following: 1) advanced age (greater than 65 years), 2) resident of a RCF and 3) recent antibiotic exposure identified as risk factors for colonisation [48]. Gram-negative bacteria are the most prevalent ABR pathogens recovered from RCF residents. For example, a cross-sectional study at a large LTCF in Boston found that 51% of sampled residents (n = 84) were colonised with multi-drug resistant Gram-negative bacteria compared to MRSA in 28% and vancomycin-resistant enterococci in 4% [17]. A longitudinal study conducted at a LTCF in Northern Ireland demonstrated similar results, with half of included residents (n = 64) positive for ESBL-E and a quarter for MRSA [40].

Antibiotic prescription in residential care facilities is frequently inappropriate in terms of indication and selection [49, 50]. This practice may negatively impact on patient outcomes by either providing insufficient antimicrobial cover or excessive risk of adverse effects such as *C. difficile* infection (CDI). CDI is endemic in LTCFs in developed countries and represents an important obstacle to care with incident rates of 2.3 cases/10,000 resident days reported [51]. There are limited data on the prevalence and impact of CDI amongst hospitalised patients in SA [52], and no data regarding *C. difficile* colonisation or CDI in LTCFs, but it may be an important problem due to widespread use of broad spectrum antibiotics and an increasingly ageing population. Studies at a Cape Town tertiary hospital found that 9 - 16% of acute diarrhoeal
illnesses were associated with *C. difficile* infection, and the annual incidence of hospital-acquired diarrhoea was much lower compared to high income countries [52, 53].

Infection prevention and control (IPC) is a major issue in LTCFs and RCFs. From the 2014 *ECDC surveillance report on ABR in Europe* [54] only 42% of the 1181 surveyed facilities had an IPC committee. The majority (76%) had a protocol for the management of MRSA and ABR organisms. Isolation rooms were not commonly available in the majority of RCFs and as such effective barrier nursing could not be provided. No data on IPC and ABR in South African RCFs is available.

**Conclusion**

A significant knowledge gap exists on ABR in Africa. Major factors including poor hygiene, lack of infection prevention and control policies, access to quality health care, sanitation, public awareness and rampant antibiotic misuse all create the perfect environment for the emergence and dissemination of ABR bacteria. It is quite possible that we may be heading back to a pre-antibiotic era where all our current available therapies will be rendered ineffective.

Current South African guidelines recommend using carbapenems as empiric therapy for suspected healthcare-associated infections, including patients from RCFs. However, there are no published data on the prevalence of colonisation or infection with antibiotic resistant bacteria amongst residents of RCFs in SA. It is critical to understand the local antibiogram in RCFs in order to optimise empiric antibiotic selection and to reduce the unnecessary use of broad spectrum antibiotics. This has the potential of translating into improved patient outcomes and a reduction in the further emergence and spread of ABR. Determining the prevalence of colonisation with multidrug-resistant organisms and *C difficile* may also inform and potentially strengthen infection control practices in South African RCFs, and may help to guide local infection prevention and control (IPC) policy, which is currently not based on local data.
CHAPTER 2: PUBLICATION-READY MANUSCRIPT

Colonisation with pathogenic drug-resistant bacteria and *Clostridioides difficile* among residents of residential care facilities in Cape Town, South Africa.

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Author contributions
JS contributed to the protocol, collected data, assisted with analysis, wrote the first draft of the manuscript; LG assisted with protocol development and edited the manuscript; KM assisted with data analysis; PN supervised the microbiological testing; CF and NdJ collected data; MM contributed to protocol development and edited the manuscript; SW conceived the study, developed the protocol, obtained funding, analysed data, edited the manuscript.

Highlights
- Extended spectrum beta-lactamase-producing bacteria detected in 22.7\% (27/119)
- Incontinence was an independent risk factor for colonisation
- Methicillin-resistant *Staphylococcus aureus* found in 8.6\% (13/152)
- *C. difficile* colonisation was low 1.7\% (2/119)
ABSTRACT

Objectives
Residential care facilities (RCFs) act as reservoirs for multidrug-resistant organisms (MDRO). There are scarce data on colonisation with MDROs in Africa. We aimed to determine the prevalence of MDROs and *C. difficile* and risk factors for carriage amongst residents of RCFs in Cape Town, South Africa.

Methods
We performed a cross-sectional surveillance study at three RCFs. Chromogenic agar was used to screen skin swabs for methicillin-resistant *Staphylococcus aureus* (MRSA) and stool samples for extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E). Antigen testing and PCR was used to detect *Clostridioides difficile*. Risk factors for colonisation were determined with logistic regression.

Results
One hundred fifty-four residents were enrolled, providing 119 stool samples and 152 sets of skin swabs. Twenty-seven (22.7%) stool samples were positive for ESBL-E, and 13 (8.6%) residents had at least one skin swab positive for MRSA. Two (1.6%) stool samples tested positive for *C. difficile*. Poor functional status (OR 1.3 (95% CI, 1.0 – 1.6)) and incontinence (OR 2.9 (95% CI, 1.2 – 6.9)) were significant predictors for ESBL-E colonisation. There was a trend towards higher MRSA colonisation in frail care areas.

Conclusion
There was high prevalence of colonisation with MDROs but low *C. difficile* carriage, with implications for antibiotic prescribing and infection control practice.

Keywords: Residential care facility, antibiotic resistance, *C. difficile*, colonization, MRSA, ESBL, infection control, antibiotic stewardship
INTRODUCTION
Antibiotic resistance (ABR) is a global public health crisis undermining the ability to treat bacterial infections. Excessive antibiotic consumption in human health and the environment may contribute to the emerging problem of ABR. [55, 56]. The increase in multidrug-resistant organisms (MDRO) has necessitated a change in empiric antibiotic prescribing practices, and patients with healthcare-associated infections, including from residential care facilities (RCFs), are now often treated with second-line broad-spectrum antibiotics [57]. It is therefore critical to risk-stratify patients for infection with MDRO to support optimal antibiotic prescribing.

Colonisation (defined as asymptomatic carriage) with MDROS is a well-established risk factor for infection with the same strain [17, 28], particularly in immunocompromised and elderly populations [29, 30]. RCFs are increasingly recognized as reservoirs for MDROS [17, 31, 32] and colonisation with MDR bacteria has been associated with outbreaks after referral of RCF residents to acute care facilities [33]. Additionally, residents of RCFs in high income countries have high rates of Clostridioides difficile (previously Clostridium difficile) colonisation [37] and are susceptible to C. difficile infection (CDI) because of advanced age and frequent antibiotic use [38].

ABR is common in South African referral hospitals. Up to 70% of Klebsiella pneumoniae bloodstream isolates are extended-spectrum beta-lactamase (ESBL) producing strains [58], defined as being resistant to beta-lactam antibiotics, including third-generation cephalosporins such as cefotaxime, ceftriaxone, and ceftazidime. Almost a quarter of Staphylococcus aureus bloodstream infections at one tertiary academic centre were resistant to cloxacillin (methicillin-resistant S. aureus, MRSA) [58]. There are no published data on the prevalence of colonisation with MDROS or C. difficile amongst residents of RCFs in South Africa, but this is needed to guide recommendations for empiric antibiotic prescribing and infection control practices in these facilities. We performed a cross-sectional microbiological prevalence survey at three RCFs in Cape Town, South Africa, to determine the prevalence of colonisation with ESBL-producing Enterobacterales (ESBL-E), MRSA and toxigenic C. difficile; and identify risk factors for colonisation.

METHODS
Study setting and population
There are approximately 30 RCFs in the Cape Town metropolitan area. The majority of these institutions are operated by a non-profit organisation, the Cape Peninsula Organisation for the Aged (CPOA), which operate 25 facilities with ~3,000 residents. We selected three CPOA facilities for inclusion in a cross-sectional prevalence survey that were broadly representative of population demographics, functional status, and access to public and private acute-care hospitals.

A random list of residents was generated at each facility, stratified by independent living and frail care areas. Frail care was defined as a specialised area in the RCF where residents require 24-hour nursing care or supervision. These residents generally require assistance with activities of daily living (e.g. washing, dressing, eating), mobilisation, and taking of medicines [59].
Residents identified from the random lists were approached for participation in the study. In addition to active recruitment, information leaflets were distributed and formal presentations were done at each facility to encourage participation. Residents (or their legal representative where appropriate) expressing interest in participating were asked to provide written/telephonic informed consent prior to enrolment.

**Sources of data**

*Risk factors for colonisation with MDROs and C. difficile*

The following demographic and clinical data were collected at a single study visit through interviews and medical record reviews: presence of faecal/urinary incontinence, presence indwelling medical device, hospital exposure within last 6 months, systemic antibiotic exposure within the last 3 months, current use of proton pump inhibitors, functional and cognitive performance, presence of any skin ulceration, medical comorbidities (using the Charlson index), and any previous microbiological results in last 6 months. These were selected because of documented and putative associations with MDROs and *C. difficile* [17, 27, 29, 32, 40, 49]. Functional performance was assessed using the Katz Index of Independence in Activities of Daily Living (Katz ADL) which evaluates ability to perform ADLs and plan selfcare [60]. Scores ≤ 2 indicate severe functional impairment, 3 - 5 mild-to-moderate impairment, and 6 indicates independence. The presence of dementia was ascertained from medical records and through clinical assessment by the study doctor combined with simple screening tools (3-word recall) and the assessment of the facility nursing staff [61, 62]. All data were collected using standardised case report forms.

**Microbiological data**

Skin swabs of nasal, axillary and inguinal areas were performed to screen for carriage of MRSA. Stool was collected from each participant to screen for colonisation with ESBL-E and toxigenic *C. difficile*. All specimens were processed at the National Health Laboratory Services (NHLS) clinical microbiology laboratory at Groote Schuur Hospital, Cape Town. Skin swabs and stool samples were plated onto chromogenic screening agar, ChromID MRSA and ChromID ESBL agar plates (bioMérieux, Marcy l’Etoile, France). After incubation, suggestive colonies were identified and antibiotic susceptibility testing was performed using the Vitek 2 System (bioMérieux), and interpreted with Clinical Laboratory Standards Institute (CLSI) 2017 criteria. We did not screen for vancomycin-resistant Enterococci due to low prevalence in South African hospitals. Although carbapenem-resistant Enterobacteriaceae were not specifically screened for, these are also detected on the ChromID ESBL agar plates. An automated nucleic acid amplification test, Xpert *C. difficile* (Cepheid, Sunnyvale, CA, USA) was initially used to screen for toxigenic *C. difficile* in stool samples. This was later changed to a two-step algorithm where samples were screened with the dual antigen (glutamate dehydrogenase (GDH) and toxins A and B) with a C. Diff Quik Chek Complete test (TechLab, Blacksburg, VA, USA). *C. difficile* carriage was defined by positivity of both GDH and toxin assays; GDH-positive and toxin-negative samples reflexed to Xpert *C. difficile* testing.
Analysis
The primary outcome measure was the proportion of residents colonised with MDROs and toxigenic *C. difficile*. Assuming a combined population of ~420 residents at the recruitment facilities, a sample size of 150 was planned to detect an ESBL-E colonisation prevalence of 20% with 5% precision. Associations between MDRO colonisation and participant characteristics were identified using the Wilcoxon rank sum test for continuous variables and $\chi^2$ test for categorical variables. Logistic regression was used to determine the risk factors associated with colonisation. Univariable analysis included the following pre-specified variables, plus significant associations identified in the descriptive analysis: hospitalisation and/or antibiotic exposure within the previous 3 or 6 months, non-ambulatory status, presence of pressure ulcers, and Charlson score. These variables were included in a multivariable model to adjust for potential confounding, using a backward stepwise selection strategy ($P < 0.2$). We combined significant predictors into risk scores by assigning a point to each variable per 1-fold increased odds of colonisation. The predictive accuracy of the score was evaluated by calculating the area under the receiver operating characteristic curve (AUROC). Analysis was performed in Stata (Version 14.2; Stata Corp, College Station, Texas, USA).

Ethics
The study was approved by the University of Cape Town Human Research Ethics Committee (reference number 806/2016).

RESULTS
Characteristics of study population
One hundred fifty-four participants were enrolled from three RCFs between March 2017 and April 2018; the cohort included 59 residents from frail care and 95 from independent living areas. Median age was 79 years (interquartile range (IQR) 74 – 86) and 111 (72%) residents were female. Thirty-seven (24%) participants were bed- or chair-bound and the majority ($n = 102, 67\%$) had Katz scores $\geq 5$, indicating limited/no functional impairment. Forty-five (29.2%) had a diagnosis of dementia; median Charlson score was 1 (IQR 0 – 2). Urinary incontinence was present in 56 (36%) of participants and faecal incontinence in 24 (16%). Median time in the residence at the time of study participation was 41 months (IQR 17 – 72). Eighteen (12%) participants had been admitted to hospital in the previous six months and 38 (25%) had received systemic antibiotics in the previous three months.

Prevalence of colonisation with MDROs and *C. difficile*
Stool samples were obtained from 119 residents. ESBL-E colonisation was detected in 27/119 (23%), comprising the following organisms: *E. coli* (17/27 isolates, 63%), *K. pneumoniae* (5/27 isolates, 19%), *E. cloacae* (4/27 isolates, 15%), and a single participant with mixed growth of *E. cloacae* and *E. coli*. Additional resistance to ciprofloxacin was detected in 19% (5/27), piperacillin-tazobactam in 11% (3/27) and gentamicin in 30% (8/27) (Figure 1). All isolates were susceptible to carbapenems.

One hundred fifty-two sets of skin swabs were collected. A set was defined as three single swabs used to sample the nares, axillae and groin from an individual participant. MRSA was
recovered from 13/152 (9%) individuals. The frequency of MRSA colonisation according to sampling site was: nasal 47%, groin 33% and axillae 20%. Four (3%, n = 117) participants had evidence of concurrent MRSA and ESBL-E colonisation.

Two (1.7%, n = 119) stool samples from asymptomatic residents were positive for *C. difficile*; both detected using the GDH antigen and toxin assay (n = 81). The remainder (n = 38) were tested using a nucleic acid amplification test with no positive results.

**Factors associated with MDRO colonisation**

A significantly higher proportion of participants colonised with ESBL-E had urinary and/or faecal incontinence (59.3% vs. 33.7% in those not colonised; P = 0.02) (Table 1). The prevalence of ESBL-E amongst participants with incontinence was 34% (16 cases, n = 47), translating into a 2.9-fold increased odds (95% CI 1.2 – 6.9) of ESBL-E colonisation with any form of incontinence. ESBL-E colonisation was also associated with lower Katz ADL scores; there was a 1.3-fold (95% CI 1.0 - 1.6; P = 0.03) increased odds of colonisation for every 1-point reduction in the Katz ADL. Incontinence remained an independent predictor of ESBL-E colonisation on multivariable analysis, adjusted odds ratio (OR) 3.2 (1.3 – 8.1) (Table 2). Half of participants with a poor functional status (Katz score ≤ 2) and incontinence were colonised with ESBL-E (53.3%; 8 cases, n=15), significantly higher and in contrast to those without either of these factors: ESBL-E colonisation 13.8% (9 cases, n=65).

However, the discriminatory value of this risk factor combination was poor with area under the curve of the receiver operating characteristics curve (AUROC) 0.67 (95% CI 55 – 78). There was a trend towards having a higher median Charlson co-morbidity score in colonised individuals (2 vs. 1 in non-colonised), although this was not statistically significant (P = 0.06). There were no other associations between pre-specified risk factors and colonisation with ESBL-E (Table 1).

As shown in Table 3, participants colonised with MRSA had resided in their respective facilities for significantly less time compared to those who were not colonised with MRSA (20.9 vs 44.2 months; P = 0.04). There was a numerically higher proportion of MRSA-colonised individuals in frail care areas (61.5% vs. 36.0% in independent living areas; P = 0.07). The prevalence of MRSA colonisation amongst those in frail care was 13.8% (8 cases, n = 58), a non-significant 2.8-fold (95% CI, 0.9 – 9.2) increased odds of MRSA compared with participants residing in independent living areas. Multivariable analysis was not performed for MRSA colonisation because of low case numbers.

**DISCUSSION**

Determining the prevalence of colonisation with MDROs and *C. difficile* amongst RCF residents is important to inform empiric antibiotic selection and infection control practices. In South Africa, guidelines for managing RCF residents with infection are not based on local data, and this knowledge gap formed the rationale for the present study. We found that amongst 154 residents at three RCFs in Cape Town, the prevalence of ESBL-E and MRSA colonisation was 23% and 8%, respectively. *C. difficile* carriage was uncommon, identified in only two participants.
Urinary or faecal incontinence and poor functional status were associated with ESBL-E carriage, and there was a trend towards increased risk of MRSA colonisation amongst residents in frail care.

There is a large amount of variability in published MDRO prevalence amongst long-term care facility residents. Estimates of ESBL-E colonisation in European series ranged between 4% and 64% [31, 32, 40, 41], similar to reports from the US [17, 27]. The wide range in prevalence is likely due to heterogeneity in study population. For example, inconsistent definitions of ‘long-term care facility’ are applied, some of which encompass acute care step down facilities expected to have higher prevalence of MDROs compared with RCFs, where residents are less sick and have less exposure to antibiotics [42-44]. ESBL-E colonisation was detected in 12% of residents (n = 119) in 3 residential aged care facilities in Australia [63]. Similar to our study the majority of residents were highly mobile and no association between recent antibiotic use, length of stay, urinary catheterisation, presence of diarrhoea and ESBL-E colonisation was found. The reported rates of C. difficile were also very low (1%), as in our study. In Belfast, Ireland, very high rates of ESBL-E colonisation (40%) were reported from 294 residents across 16 nursing homes; in contrast to our study, residents generally had high exposure to systemic antibiotic therapy, which was a significant risk factor for colonisation with ESBL-E [46].

These observations support our hypothesis that, based on the epidemiology of MDROs in acute care facilities in South Africa, the local prevalence of colonisation in RCFs would be similar to that in high income settings. This high prevalence of ESBL-E colonisation (23%), plus additional resistance to ciprofloxacin (18%) amongst residents from RCFs in Cape Town suggests risk of treatment failure with the use of third generation cephalosporins and quinolones for common infection syndromes such as urinary tract infection and possibly pneumonia (as most pneumonia is frequently caused by Gram-positive bacteria).

Our findings are consistent with others showing Gram-negative bacteria to be the most prevalent multi-resistant pathogens recovered from RCF residents. For example, a cross-sectional study at a large LTCF in Boston found that 51% of sampled residents (n = 84) were colonised with multi-drug resistant Gram-negative bacteria compared to MRSA in 28% and vancomycin-resistant enterococci in 4% [17]. A longitudinal study conducted at a LTCF in Northern Ireland demonstrated similar results, with half of included residents (n = 64) positive for ESBL-E and a quarter for MRSA [46].

Poor functional status (i.e. residents requiring assistance with ADLs) and impaired mobility, with or without dementia, have been identified as significant factors for ESBL-E and MRSA colonisation [32]. In our study poor functional status (i.e those with a low Katz ADL score) and any form of incontinence were significantly associated with ESBL-E colonisation. The prevalence of ESBL-E colonisation with the combination of incontinence and Katz score ≤ 2 was high (53%), but had poor discriminatory value. Similar observations have been reported from high-income countries. In a study from Melbourne, Australia, where 115 residents from 4 facilities were screened, faecal incontinence and significant functional dependence (low Katz ADL score) were
also shown to be major factors for colonisation with MDROs [64]. Similar predictors for MDR Gram-negative colonisation were found in a LTCF cohort in Boston: faecal incontinence, need for assistance with ADLs, advanced dementia and residing in units where more intensive nursing care was provided [17]. These factors may lead to higher levels of staff contact which result in cross-transmission [65]. It has been suggested that intensified infection prevention and control (IPC) measures, such as wearing of gowns and gloves by healthcare workers [66] and enhanced hygiene practices should be implemented for residents at high risk for MDRO colonisation [67]. Screening for ESBL-E and isolation of carriers outside of outbreak settings is controversial, and more evidence is required to understand the impact of this strategy to prevent transmission [68].

A comparatively low prevalence of MRSA colonisation (9%) was seen in our cohort, in contrast to studies in high income settings where MRSA prevalence ranged between 16% and 50% in various LTCF populations [34, 35], [36]. This discrepancy may be a consequence of circulating epidemic MRSA strains in the United States [69], which has not been the case in South Africa [70]. Shorter median time spent in RCFs was associated with MRSA colonisation in our study (20.9 versus 44.2 months for those not colonised). This may have been a chance finding due to low case numbers, and is susceptible to confounding factors which could not be adjusted for, such as visits to acute care facilities, which increases risk of MRSA acquisition [27], and differences in antibiotic therapy and IPC practices of attending physicians. There was a trend towards higher MRSA colonisation amongst residents in frail care; this has been observed in other settings and is possibly related to more frequent use of invasive medical devices, chronic wounds, and antibiotic exposure in this population [71].

CDI is endemic in RCFs in high income countries with incidence rates of 2.3 cases/10,000 resident days reported [51]. In contrast, only 2/119 (< 2%) samples were positive for *C. difficile* in our study. Studies at a Cape Town tertiary hospital found that 9 - 16% of acute diarrhoeal illnesses were associated with *C. difficile* infection, and the annual incidence of hospital-acquired diarrhoea was much lower compared to high income countries [72, 73]. These observations reflect the wide prevalence ranges for *C. difficile* which has a complex epidemiology across different settings, influenced by strain type, infection control and prescribing practices [45, 74, 75]. Active surveillance for carriers of toxigenic *C. difficile* has been advocated in high burden settings [76], but our findings suggest this may not be necessary in South African RCFs.

Our study has several limitations. As a result of limited resources we could not recruit residents from all RCFs in Cape Town, and selected a subset on the basis of representative demographics. Further limiting generalisability, we were unable to include all residents from the three participating facilities, and there were imbalances in number of participants across the RCFs. Although we generated randomised lists of residents at each facility, there is inherent bias in the recruitment process, and residents with MDRO colonisation may have been systematically excluded. We attempted to preferentially enrol residents in frail care areas in order to capture the highest risk group, but consent was more challenging in this population, skewing the sample towards independent living and less functional impairment. Our power to detect
associations with MDRO colonisation was limited by low prevalence of MRSA colonisation, and because only 77% (119/154) of participants were willing to provide stool samples for ESBL-E screening. Although reliable systems were in place to collect clinical data, antibiotic exposure may have been underestimated as medications received during hospital admissions and clinic/general practitioner visits were incompletely documented. Finally, data collection occurred over a prolonged period due to logistic limitations and this may have influenced our results as colonisation prevalence is known to change over time [77].

Notwithstanding these limitations, our survey demonstrated a high prevalence of colonisation with MDROs but low C. difficile carriage amongst residents of RCFs in Cape Town, South Africa. This has important implications for practice, including review of local antibiotic prescribing guidelines to ensure appropriate initial therapy for RCF residents. Crucially, IPC interventions such as improved healthcare worker hand hygiene and barrier nursing, as well as antibiotic stewardship, should be implemented, and possibly targeted at higher risk residents, including those with incontinence and lower functional status, to interrupt the transmission of MDROs in RCFs.

ACKNOWLEDGEMENTS
We would like to thank Colleen Roux at the Cape Peninsula Organisation for the Aged (CPOA) for allowing access to their facilities and for supporting this study. We are very grateful to Denese Jonkers and Gloria Mhlambo at Arcadia Place and Nodoza Msadu at Avondrust. Our sincere thanks also to Harris Burman, Timo Freeth, Ingrid Zass, and Colette Longworth at Highlands House. We thank staff at the Groote Schuur Hospital NHLS microbiology laboratory for their assistance with study specimens.

FUNDING SOURCES
This work was supported by research grants from the Federation of Infectious Diseases Societies of Southern Africa-GlaxoSmithKline as well as the International Society for Infectious Diseases. SW is supported by the European & Developing Countries Clinical Trials Partnership (Grant number CDF1018) and Wellcome Trust (Grant number 203135/Z/16/Z). The funders had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

DECLARATIONS OF INTEREST
None.
REFERENCES


Table 1. Associations with extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) colonisation

<table>
<thead>
<tr>
<th></th>
<th>Colonised (n = 27)</th>
<th>Not colonised (n = 92)</th>
<th>Prevalence ESBL-E (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility 1</td>
<td>15 (55.6)</td>
<td>33 (35.9)</td>
<td>31.2</td>
<td>0.109</td>
</tr>
<tr>
<td>Facility 2</td>
<td>12 (44.4)</td>
<td>53 (57.6)</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>Facility 3</td>
<td>0 (0)</td>
<td>6 (6.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Time in facility, months</td>
<td>43.9 (22.9 – 65.2)</td>
<td>40.7 (14.3 – 73.6)</td>
<td>NA</td>
<td>0.992</td>
</tr>
<tr>
<td>Frail care resident</td>
<td>12 (44.4)</td>
<td>26 (28.3)</td>
<td>31.6</td>
<td>0.113</td>
</tr>
<tr>
<td>Any incontinence</td>
<td>16 (59.3)</td>
<td>31 (33.7)</td>
<td>34.0</td>
<td>0.017</td>
</tr>
<tr>
<td>Hospital exposure in last 6 months</td>
<td>10 (37.0)</td>
<td>21 (22.8)</td>
<td>32.3</td>
<td>0.139</td>
</tr>
<tr>
<td>Systemic antibiotic exposure last 3 months</td>
<td>8 (29.6)</td>
<td>18 (20.0)</td>
<td>30.8</td>
<td>0.291</td>
</tr>
<tr>
<td>Previous positive culture from a clinical specimen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (36.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 (39.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25.9</td>
<td>0.856</td>
</tr>
<tr>
<td>Bedbound or chair-bound</td>
<td>9 (33.3)</td>
<td>17 (18.5)</td>
<td>34.6</td>
<td>0.100</td>
</tr>
<tr>
<td>Katz score: median (ranges)</td>
<td>6 (2-6)</td>
<td>6 (4-6)</td>
<td>NA</td>
<td>0.048</td>
</tr>
<tr>
<td>Dementia</td>
<td>10 (37.0)</td>
<td>20 (21.7)</td>
<td>33.3</td>
<td>0.107</td>
</tr>
<tr>
<td>Charlson index score</td>
<td>2, (1-2)</td>
<td>1, (1-2)</td>
<td>NA</td>
<td>0.058</td>
</tr>
<tr>
<td>Currently using PPI</td>
<td>8 (29.6)</td>
<td>19 (20.6)</td>
<td>19.6</td>
<td>0.090</td>
</tr>
</tbody>
</table>

Data are median or n (percent). PPI, proton pump inhibitor

<sup>a</sup> Includes microbiological evidence of *S. aureus, Enterobacterales, C. difficile*

<sup>b</sup> n = 19

<sup>c</sup> n = 51
Table 2. Univariable and multivariable analysis of risk factors associated with extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) colonisation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariable</th>
<th>Multivariable (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Any incontinence</td>
<td>2.9 (1.2 – 6.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>Katz ADL</td>
<td>1.3 (1.0 – 1.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Systemic antibiotic exposure last 3 months</td>
<td>1.7 (0.6 – 4.5)</td>
<td>0.294</td>
</tr>
<tr>
<td>Hospital exposure in last 6 months</td>
<td>1.9 (0.8 – 4.9)</td>
<td>0.143</td>
</tr>
<tr>
<td>Non-ambulatory</td>
<td>2.2 (0.8 – 5.7)</td>
<td>0.105</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.4 (0.9 – 2.2)</td>
<td>0.119</td>
</tr>
</tbody>
</table>

Katz ADL (Activity of Daily Living) score, antibiotic exposure, non-ambulatory status, and Charlson score were removed from the multivariable model due to P-value exceeding including pre-defined inclusion threshold (P < 0.2). Presence of pressure ulcers was not included as a predictor due to insufficient data (n = 4).
Table 3. Associations with methicillin resistant *Staphylococcus aureus* (MRSA) colonisation

<table>
<thead>
<tr>
<th></th>
<th>Colonised (n = 13)</th>
<th>Not colonised (n = 139)</th>
<th>Prevalence of MRSA (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility 1</td>
<td>6 (46.2)</td>
<td>55 (39.6)</td>
<td>9.8</td>
<td>0.167</td>
</tr>
<tr>
<td>Facility 2</td>
<td>5 (38.5)</td>
<td>78 (56.1)</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Facility 3</td>
<td>2 (15.4)</td>
<td>6 (4.3)</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td><strong>Time in facility, months</strong></td>
<td>20.9 (17.3 - 36.4)</td>
<td>44.2 (17.6 - 76.7)</td>
<td>NA</td>
<td>0.042</td>
</tr>
<tr>
<td>Frail care resident</td>
<td>8 (61.5)</td>
<td>50 (36.0)</td>
<td>13.0</td>
<td>0.070</td>
</tr>
<tr>
<td>Any incontinence</td>
<td>5 (38.5)</td>
<td>57 (41.0)</td>
<td>8.1</td>
<td>0.858</td>
</tr>
<tr>
<td>Hospital exposure in last 6 months</td>
<td>2 (15.4)</td>
<td>39 (28.1)</td>
<td>4.9</td>
<td>0.325</td>
</tr>
<tr>
<td>Systemic antibiotic exposure last 3 months</td>
<td>3 (25.0)</td>
<td>35 (25.6)</td>
<td>7.9</td>
<td>0.967</td>
</tr>
<tr>
<td>Previous positive culture from a clinical specimen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 (50)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33 (40.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10.8</td>
<td>0.592</td>
</tr>
<tr>
<td>Mobility status (bedbound/chair bound)</td>
<td>5 (38.5)</td>
<td>32 (23.0)</td>
<td>13.5</td>
<td>0.215</td>
</tr>
<tr>
<td>Katz score: median (ranges)</td>
<td>5.5 (4-6)</td>
<td>6 (3-6)</td>
<td>NA</td>
<td>0.766</td>
</tr>
<tr>
<td>Dementia</td>
<td>4 (30.8)</td>
<td>41 (29.5)</td>
<td>8.9</td>
<td>0.923</td>
</tr>
<tr>
<td>Charlson index score</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>NA</td>
<td>0.848</td>
</tr>
<tr>
<td>Currently using PPI</td>
<td>3 (23.1)</td>
<td>10 (7.2)</td>
<td>8.1</td>
<td>0.701</td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (percent). PPI, proton pump inhibitor

<sup>a</sup> Includes microbiological evidence of *S. aureus*, Enterobacteriaceae, *C. difficile*

<sup>b</sup> n = 8

<sup>c</sup> n = 82


Figure 1. Susceptibility of extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E) isolates to commonly-used antibiotics
Appendices
1. Human Research and Ethics Committee approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

11 November 2016

HREC REF: 886/16

Dr S Wasserman
Infectious Diseases and HIV Medicine
G25.63
N031

Dear Dr Wasserman,

PROJECT TITLE: PREVALENCE OF AND RISK FACTORS FOR COLONIZATION WITH PATHOGENIC DRUG-RESISTANT BACTERIA AND C. difficile AMONG RESIDENTS OF LONG AND MEDIUM-TERM CARE FACILITIES IN CAPE TOWN (PREDICT). (MPhil candidate: Dr JH September)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the proof of concept for phase 1 of the above-mentioned study.

Approval is granted for one year until the 30th November 2017. This is subject to receiving the approvals from all the sites where recruitment will occur.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Dr JH September will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely,

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
2. Participant consent form (English)

Prevalence of and risk factors for colonisation with pathogenic drug-resistant bacteria and *C. difficile* among residents of long- and medium-term care facilities in Cape Town (PREDICT)

**PARTICIPANT CONSENT**

By signing below, I agree that:

- I have read the information sheet, which is written in a language with which I am fluent and comfortable, or which has been adequately translated.
- I have had the chance to ask questions and they have been answered.
- I understand that taking part in this study is voluntary.
- I give permission to use and share my health data and all confidential information as described in the information sheet.
- I may choose not to be in the study or to leave the study at any time by telling the study doctor or nurse.
- If I leave the study for any reason, the study team may still use some of my information collected up to that point.

<table>
<thead>
<tr>
<th>Name of participant</th>
<th>Signature/thumbprint</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of person conducting consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the case of verbal consent, an impartial witness verifies that informed consent was obtained from the above participant. The participant has been informed about the risks and the benefits of the research, understands such risks and benefits and is able to give consent to participation, without coercion, undue influence or inappropriate incentives.

<table>
<thead>
<tr>
<th>Name of impartial witness</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Proxy consent form (English)

UNIVERSITY OF CAPE TOWN

Prevalence of and risk factors for colonisation with pathogenic drug-resistant bacteria and C. difficile among residents of long- and medium-term care facilities in Cape Town (PREDICT)

CONSENT FORM FOR NEXT OF KIN OR LEGAL PROXIES OF RESIDENTS/PATIENTS WHO ARE UNABLE TO PROVIDE CONSENT

I ........................................................................................................ (hereafter known as the proxy) am the proxy for

........................................................................................................ (hereafter known as the resident).

I am related to the resident in the following way:

........................................................................................................ and through this relationship
I am able to act on behalf of the resident who is unable to provide consent for
the following reason ........................................................................................................

As the legally appointed proxy or next of kin*, I am able to assist

........................................................................................................ in making a decision to
participate in this study.

Confirmation of Relationship to Resident or Legal Evidence of Proxy Status

Identify document

Drivers license

Passport

Documentation of curator persona or curator bonis

*Acceptable next of kin includes: spouse or partner, adult child, adult sibling

In the case of verbal consent, an impartial witness verifies that the above proxy was contacted and provided the above information.

_________________________________________  __________________________  ___________
Name of impartial witness  Signature  Date

PREDICT study: Proxy ICF V1.0
Prevalence of and risk factors for colonisation with pathogenic drug-resistant bacteria and *C. difficile* among residents of long- and medium-term care facilities in Cape Town (*PREDICT*)

This pamphlet provides information about a research study taking place at your institution. The study is being conducted by researchers from the Divisions of Infectious Diseases and Geriatric Medicine at the University of Cape Town, and has been approved by the management of your institution as well as by the UCT ethics committee (Ref: xx/2016). The study is funded by the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) and the International Society for Infectious Diseases (ISID).

**Purpose and aims of the study**

In order to decide on the best treatment for people with suspected infections, it is important to know the types of bacteria that are causing infections and whether they are resistant to the usual antibiotics. People living in places like retirement homes and other long- or medium-term care facilities may be at higher risk of getting infections with resistant bacteria because of more frequent hospitalisations and antibiotic use. They may also be at higher risk of developing diarrhoea after using antibiotics because of a bacteria called *C. difficile*.

In Cape Town (and South Africa in general) we do not know what this risk is and therefore are not able to make the most informed decisions about antibiotic choices for this population. Every person, even those who are healthy, carries bacteria on their skin and in their gut, and knowing the types of these so-called “colonising” bacteria and their resistance profiles will help us to decide what antibiotics to choose in the case of an infection.

The aim of this study is to understand the frequency of, and risk factors for, carriage of resistant bacteria and *C. difficile* among people living in retirement homes and a medium-term care facility in Cape Town. This will allow doctors to choose more appropriate antibiotics when people from similar settings require treatment for a suspected infection. Ultimately this will lead to improved treatment, and possibly better infection control practices.

**Where will the study take place and how many people will participate?**

We will be conducting the study at Highlands House plus a COPA residential care facility, as well as at Booth Memorial Hospital, a post-acute care facility in Cape Town. We are planning to include about 270 participants from the three facilities.

**Who will be included in the study?**

All residents and patients of the three facilities will be eligible to participate. Members of the study team, or your doctors, will approach you (or your next of kin or legal proxy where appropriate) to discuss participation after randomly drawing your name from the list of residents. We will offer participation to everyone on the list until we have reached our enrolment target. You may also request to participate by asking your doctor. Before participating in the study we will ask you (or your next of kin or legal proxy where appropriate) to sign an informed consent document confirming that you have read and understood the study as described in this information sheet.

*PREDICT study: Information Sheet V1.0*
How long will the study last?
Your participation in the study will require around half an hour of your time at a single visit. We are aiming to complete the study over 3 to 6 months in 2017.

What will happen if you decide to take part in the study?
There will be 3 main procedures which will be performed by trained and experienced study staff:

1. We will ask you some questions to assess your overall health status. This will include questions relating to your medical conditions, previous hospital admissions, and functional ability. We will also request information about your previous antibiotic use. We will ask permission to access your medical records to confirm these details.

2. We will collect swabs from skin around your nose, groin and armpit areas using an instrument similar to a cotton bud. This is to test for bacteria called *Staphylococcus aureus* that live on the skin of some people in these areas. The procedure is completely painless and carries no risk, and should take under 3 minutes to complete.

3. We will ask you to provide a stool sample to test for other types of resistant bacteria as well as an organism called *C. difficile*. For this, we will provide you with a container that you can use to collect a stool sample in; your regular nurses or the study nurse will be available to assist you with this if you wish. You may provide this at any time after agreeing to participate in the study. Alternatively, if you prefer not to provide a stool sample, we can perform a cotton swab of your rectal area. This will involve inserting the soft cotton tip of the narrow swab into the bottom part of your rectum. The procedure is slightly uncomfortable but should not cause any pain, and takes about 10 seconds. The risks of injury associated with this procedure are extremely low, but may include minor bleeding.

What will we do with the samples?
All swabs will be transported to the National Health Laboratory Service (NHLS) clinical microbiology laboratory at Groote Schuur Hospital where they will be processed and tested. The laboratory will store the bacteria recovered to conduct additional tests in the future, including a determination of the resistance genes of the bacteria. This does not contain any information about you, or relate to your personal health in any way.

Are there any benefits to you for being in the study?
By participating in this study you will be contributing to knowledge of antibiotic resistance, and this may allow us to better treat residents and patients of retirement homes and medium-term care facilities who become ill with suspected bacterial infection. We will also share the results of the with your medical team, and you will therefore know if you are colonised with resistant bacteria or *C. difficile*, and this could directly impact on your treatment if you were to get an infection in the future.
What if you choose to withdraw from the study?
Your decision to participate in this study is voluntary. You can choose at any time to withdraw from the study by telling the study doctor or nurse, without any penalty. Even if you have initially agreed to participate you may leave the study at any time, or decline to participate in any of the individual procedures. This will have no impact on your continued care.

Who will see the information which is collected about you during the study?
The information we collect will be securely stored both on paper and on computer, with access limited to the researchers. To protect your privacy, the information will be labelled in a way that will not identify you; we will assign a code to you, and your information and samples will be known only by that code. You will not be identified by name in any published reports about this study.

What if something goes wrong?
The University of Cape Town has insurance cover for the event that research-related injury or harm results from your participation in the study. The insurer will pay all reasonable medical expenses in accordance with the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation. You will not be required to prove fault on the part of the University.

Who do you speak to (or contact) if you have any questions about the study?
You may speak to any member of the study team, your doctor, or facility management about any aspect of the study. The principal investigator is Dr Sean Wasserman who can be contacted on 0214049111 or email sean.wasserman@uct.ac.za if you have any study related queries. If you have any questions or concerns about your rights or welfare as a research participant you may contact the Faculty of Health Sciences Human Research Ethics Committee (HREC) at the following address:

University of Cape Town
Human Research Ethics Committee (UCT HREC)
E 52, Room 24, Old Main Building,
Groote Schuur Hospital, Observatory
Tel: +27 21 406 6492
Fax: +27 21 406 6411
5. Study information pamphlet (Afrikaans)

**UNIVERSITY OF CAPE TOWN**

**Voorkoms van en Risikofaktore vir die Kolonisasie met Patogeniese Medisnebestandige Bakterieë en *Clostridium difficile* onder Inwoners van 'n Lang- en Medium Termyn Sorgfasiliteit in Kaapstad (PREDICT)**

Hierdie pamphlet verskaf inligting in verband met 'n navorsingstudie wat plaasvind by ons instituut. Die studie word gedoen deur navorsers van die Divisie van Infectieuwe Siektes en Geriatriese Medisynne aan die Universiteit van Kaapstad. Die studie was goedgekeur deur ons instituut, sowel as Universiteit van Kaapstad te etiese komitee (Verwysing: xx/2016). Die studie word gefinansier deur die Federasie van Aansteeklike Siektes Vereniging van Suid-Afrika (FIDSSA) en die Internationale Vereniging van Aansteeklike Siektes.

**DOEL EN UITKOMS VAN DIE STUDIE**

Om die beste individuele behandeling te verskaf, is dit belangrik om uit te vind watter tipe bakterieë sekere siektes veroorsaak en watter bakterieë weerstandig is teen sekere antibiotika. Mense wat in aftreeoorde soos lang- en mediumtermyn sorgfasiliteite bly, het 'n groter risiko om met weerstandige bakterieë geïnfecteer te word as gevolg van gereeldes hospitalisasie en antibiotika behandeling. Hulle het ook 'n groter risiko om diarree te ontwikkel na antibiotika gebruik, wat veroorsaak word deur die organismes *Clostridium Difficile*.

In Kaapstad (en Suid Afrika oor die algemeen) weet ons nie wat die risiko is nie en daarmee kan ons nie ingeligte besluite maak oor die beste keuse van antibiotika vir die populasie nie. Elke persoon, insluitend dié wat gesond is, dra bakterieë op hulle vel en ingewande. In die geval van 'n infeksie, help dit met die akkurate keuse van antibiotika indien die koloniserende bakterie bekend is. Bogenoende inligting sal dokters help met die keuse van antibiotika indien 'n persoon van dieselde inrigting behandeling benodig vir 'n veroorde infeksie. Dit sal hydra tot optimale behandeling en hopelik beter infeksie bekämping.

**WAAR GAA DIE STUDIE PLAASVIND, EN HEOEVEL MENSE GAAN DEELNEEM AAN DIE STUDIE?**

Die studie gaan plaasvind by Highlands House en twee “Cape Peninsula Organisation for the Aged (CPOA)” verblyf fasilitete: Arcadia Place en Avondrust. Ons beoog om 270 kandidate in die drie fasilitete te nader.

**WIE GAAN INGESLUIT WORD IN DIE STUDIE?**

Enige inwoner en/of patiënt van die drie fasilitete kan deelneem. Lede van die studie groep, of u dokters, sal u benader (of u naasbestaande; of wettig deur proxy waar toepaslik) om deelname te bespreek, nadat u naam blindelings uit 'n lys gekies word. Ons sal deelname aan elke individu aanbied totdat ons die inskrywingsdoel bereik.

U mag ook u dokter vra om deel te neem. Ons sal u naasbestande vra om 'n ingeligte toestemmingsoorm te teken indien u besluit om deel te neem; dit sluit in dat u die reëls en regulasies deeglik deurgelees het en dit verstaan.
HOE LANK GAAN DIE STUDIE NEEM?
U deelname in die studie sal omtrent 'n halfuur duur met 'n enkele besoek. Ons beoog om die studie oor die afloop van 3 tot 6 maande in 2017 te voltooi.

WAT GAAN GEBEUR INDIEN U BESLUIT OM DEEL TE NEEM AAN DIE STUDIE?
Daar gaan 3 hoof prosedures plaasvind, wat uitgeoer sal word deur ervare en opgeleide personeel:

1. Ons gaan u 'n paar vrae vra om omtrent u algehele gesondheid. Dit sal vrae insluit aangaande u mediese kondisie, vorige hospitalisasie en funksionele vermoeë. Ons sal ook inligting vra in verband met onlangs antibiotika gebruik. Ons sal toestemming vra vir toegang tot u mediese rekords.

2. Ons gaan deppers, soortgelyk aan 'n orstokkie is, neem van u neus, onderarm en lies om te toets vir die organisme Staphylococcus aureus, wat in hierdie areas op mense se vel leef. Hierdie prosedure is pynloos, risiko-vry en sal omtrent 3 minute duur.

3. Ons gaan ook 'n stoelgang monster kollekte sodat ons vir ander tipes weerstandige bakteriëë, soos byvoorbeeld C. Difficile, kan toets. Om laasgenoemde te doen sal ons aan u die hoer verskaf waarin u die stoelgang kan kollekte. U daagliks verpleegsters sal u hiermee help. U mag dit enige tyd verskaf tydens die studie. Andersins, indien u nie 'n stoelgang monster wil gee nie, kan ons 'n monster deur middel van 'n depper-stokkie in die rektale area neem. Dit is basies om die sagte gedeelte van 'n wattedepper te neem en in die laagste gedeelte van die rektum te sit. Hierdie prosedure is ongemaklik maar pynloos en behoort omtrent 10 sekondes te duur. Die risiko van hierdie prosedure is baie laag, maar kan ligte bloeding tot gevolg hê.

WAT GAAN ONS MET DIE MONSTER DOEN?
Elke depper sal vervoer word na die Nasionale Gesondheids Laboratory Dienste, wat 'n kliniese en- mikrobiologiese laboratorium te Groote Schuur Hospitaal is waar dit prosesseer en getoets sal word. Die laboratorium sal die organisme wat groei bewaar, sodat verdere studies daarop gedoen kan word, veral die bepaling van weerstandige gene van bakteriëë. Dit sal nie enige van u informasie bevat nie, en sal nie ooreenstem met u persoonlike gesondheid nie.

IS DAAR ENIGE VOORDELE VIR U AS PERSOON, INDIEN U AAN DIE STUDIE DEELNEEM?
Deur u deelname sal u bydra tot die kennis van antibiotika-weerstandighed en ons so toelaat om inwoners van ouetehuisie en medium- en langtermyn sorgfasiliteite, wat seei word met vermoede bakteriële infeksie, beter te behandel. Ons sal ook die resultate bekend maak aan u mediese span, sodat u sal weet indien u gekoloniseer is met 'n weerstandige bakterie of C. diff, wat 'n direkte impak op u behandeling het sal hê, indien u siek raak in die toekoms.
WAT AS JY BESLUIT OM TE ONTREK UIT DIE STUDIE?
U besluit om deel te neem aan die studie is vrywillig. U kan enige tyd tydens die studie kies om te ontrek deur u mediese dokter of verpleegster in kennis te stel, sonder enige straf. Alhoewel u oorspronklik besluit om deel te neem, mag jy enige tyd tydens die verloop van die studie ontrek en mag u ook weier om deel te neem aan enige prosedure. Hierdie keuse sal geen impak op u toekomstige sorg hé nie.

WIE GAAN DIE INLIGTING WAT TYDENS DIE STUDIE VAN JOU KOLLEKTEER WAS SIEN?
Die inligting wat ons versamel gaan veilig gestoor word op beide papier en rekenaar; slegs die navorsers het toegang tot die inligting. Om u privaatheid te beskerm sal die monsters gemerk word op 'n manier waarmee u nie identifiseer kan word nie. U sal 'n kode kry, en u informasie en monsters sal alleenlik deur 'n kode herken word. U sal nie geïdentifiseer word deur u naam tydens die studie nie.

WAT AS IETS VERKEERD LOOP?
Die Universiteit van Kaapstad het versekeringsdekking in die geval van navorsing-afhanklike besering en -beskadiging vir u deelname gedurende die studie. Die versekering sal alle redelike mediese onkostes betaal in verband met Suid Afrikaanse Goeie Kliniese Praktiserende Riglyne (DOH 2006), gebaseer op die Assosiasie van Britse Farmasieetiese Industrie Riglyne, in die geval van besering of newe-effek wat 'n direkte resulataat van u deelname is. U sal nie die universiteit kan blameer nie.

INDIEN U ENIGE VRAE HET IN VERBAND MET DIE STUDIE, WIE KAN U BEL OF KONTAK?
U mag met enige lid van die navorsingspan, u dokter, of faciliteitsbestuurder praat oor enige aspekt van die studie. Die hoofnavorser is Dr Sean Wasserman, wat u kan skakel op 0214049111, of e-pos sean.wasserman@uct.ac.za, indien u enige vrae het oor die studie. Indien u enige vrae of bekommernisse het oor u regte en welstand as 'n navorsingsdeelnemer, mag jy die Fakulteit van Gesondheidswetenskappe Menslike Navorsingsetiesie Komitee kontak by die volgende adres:

Universiteit van Kaapstad
Menslike Navorsingsetiesie Komitee
E52, KAMER 24, QU HOOF GEBOU
GROOTE SCHUUR HOSPITAAL, OBSERVATORY
TEL: +27 21 404 6492
FAX: +27 21 404 06411
**6. Participant consent form (Afrikaans)**

**UNIVERSITY OF CAPE TOWN**

**VOORKOMS VAN EN RISIKOFAKTORE VIR KOLONISASIE MET PATOGENIESE MEDISYNEBESTANDIGE BAKTERIEË EN CLOSTRIDIUM DIFFICILE (C. DIFFICILE ) ONDER INWONERS VAN LANG - EN MEDIUM TERMYN SORG FASILITEITE IN KAAPSTAD (PREDICT)**

**DEELNEMER TOESTEMMING**

**DEUR DIE VOLGENDE TE ONDERTEKEN, STEM EK SAAM DAT:**

1. Ek die informasie pamflet, wat geskryf is in ‘n taal wat ek vlot kan praat en gemaklik mee is, deeglik deurgelees het en dat die pamflet toepaslik vertaal is.

2. Ek die kans gekry het om vrae te vra, wat ook beantwoord was.

3. Ek verstaan dat deelname aan hierdie studie uit vrye keuse is.

4. Ek toestemming gee vir die gebruik en verspreiding van my mediese data en private informasie, soos verduidelik in die informasie pamflet.

5. Ek ten enige oomlik kan besluit om te onttrek vanuit deelname aan die studie of kan kies om nie deel te neem nie, deur die studente dokter of die verpleegster in kennis te stel.

6. As ek die studie vir enige rede verlaat, kan die navorsingspan steeds my inligting gebruik wat verskaf was tot op daardie punt.

__________________  __________________________  _______
Naam van deelnemer  Handtekening / Vingerafdruk  Datum

__________________  __________________________  _______
Naam van persoon wat  Handtekening / Vingerafdruk  Datum  toestemming neem
7. Proxy consent form (Afrikaans)

UNIVERSITY OF CAPE TOWN

VOORKOMS VAN EN RISIKO FAKTORE VIR KOLONISASIE MET PATOGENIESE MEDISYNEBESTANDIGE BAKTERIEË EN CLOSTRIDIUM DIFFICILE (C. DIFFICILE) ONDER INWONERS VAN LANG- EN MEDIUM TERMYNSORG FASILITEITE IN KAAPSTAD (PREDICT)

Toestemmingsvorm vir naasbestaande of wettig volmagthouer van die inwoner wat nie toestemming kan gee nie

Ek .............................................................................................................................. (hiermee bekend as die wettig volmagshebber persoon) het volmag vir ............................................................................................................................
(hiermee bekend as die inwoner).

Ek is verband aan die inwoner op die volgende wyse:
........................................................................................................................ en is as gevolg van hierdie verhouding in staat om namens die inwoner toestemming te gee, wat self nie toestemming kan gee nie vir die volgende rede:
........................................................................................................................
As die wettig aangestelde volmagshebber of naasbestaande, is ek bereid om ........................................................................................................ te help met die besluitneming om deel te neem aan die studie.

Bevestiging van die verhouding met inwoner of wettige bewyse van volmagsheibLIKE status.

1. Identiteitsdokument
2. Bestuurderslisensie
3. Paspoort
4. Dokumentasie van kurator persona of kurator bonis
*’n Aanvaarbare naasbestaande sluit in: gade of vennoot, volwasse kind; volwasse broer of suster. In die geval van verbale toestemming, sal ’n onpartydige getuienis bevestig dat die bogenoemde volmagtigde gekontak was en verskaf was met bogenoemde inligting.

<table>
<thead>
<tr>
<th>NAAM VAN ONPARTYDIGE GETUIENIS</th>
<th>HANDTEKENING</th>
<th>DATUM</th>
</tr>
</thead>
</table>

**DEUR DIE VOLGENDE TE ONDERTEKEN, STEM EK SAAM DAT:**

1. Ek die informasie pamflet, wat geskryf is in ’n taal wat ek vlot kan praat en gemaklik mee is, deeglik deurgelees het en dat die pamflet toepaslik vertaal is.
2. Ek die kans gekry het om vrae te vra, wat ook beantwoord was.
3. Ek verstaan dat deelname aan hierdie studie uit vrye keuse is en van my af hang.
4. Ek toestemming gee vir die gebruik en verspreiding van die inwoner / pasiënt se mediese data en private informasie, soos beskryf in die informasie pamflet.
5. Ek enige oomlik kan besluit, ter wille van die inwoner of pasiënt, om nie deel te neem nie, of te onttrek uit die studie deur die studente dokter of verpleegster, op enige oomblik, in kennis te stel.
6. Indien die inwoner / pasiënt die studie verlaat vir een of ander rede, die navorsingspan steeds van die inligting kan gebruik, wat tot op daardie punt verskaf was.

**Inwoner / pasiënt naam** ………………………………………………………………………………………………………………………………………………………………………

<table>
<thead>
<tr>
<th>Naam van volmagtigde persoon</th>
<th>Handtekening</th>
<th>Datum</th>
</tr>
</thead>
</table>

Vehouding tot die pasiënt ……………………………………………………………………………………………………………………………………………………………………… (drukskrif asseblief).

<table>
<thead>
<tr>
<th>Naam van persoon wat die toestemming neem</th>
<th>Handtekening</th>
<th>Datum</th>
</tr>
</thead>
</table>

Ek het die doel en natuur van die studie ten volle aan die deelnemer verduidelik. In die geval van verbale toestemming, sal ’n onpartydige getuienis bevestig dat ingeligte toestemming van die bogenoemde persoon verkry was. Die volmagtigde persoon was ingelig oor die gevare en voordele van die navorsingsprojek en het dit verstaan en is nogtans bereid om toestemming te gee vir deelname, uit vrye keuse en sonder onbehoorlike beïnvloeding of onvanpaste aansporing.

<table>
<thead>
<tr>
<th>Naam van onpartydige getuienis</th>
<th>Handtekening</th>
<th>Datum</th>
</tr>
</thead>
</table>
8. Case report form

**PREDiCT CRF V1.0 Feb 2017**

Date ........../........../........
Study ID
Facility Name (1=HH, 2=Booth, 3=CPOA)

**Demographics**

1. Initials........................................................................................................
2. Date of birth ................................................................. ........../........../........
2. Gender (1=male, 2=female)........................................................................
3. Race........................................................................................................
   (1=Coloured, 2=Black, 3=White, 4=Asian, 5=other: specify____________________)

**Facility details**

4.1 Date admitted/moved to facility ........................................... ........../........../........
4.2 Which section of the facility do you live in ........................................
   (1=general living area, 2=frail care area, 9=N/A (not in RCF))

**CLINICAL DETAILS**

Continence

5.1 Faecal incontinence........................................................................
5.2 Urinary incontinence

**Indwelling medical devices**

6.1 Urinary catheter

6.2 NG tube

6.3 PEG

6.4 IV line

6.5 Intermittent catheterisation

6.6 Other (specify)

**Hospital exposure in the previous 6 months**

7.1 Emergency department visit (<24 hours)

7.2 Admitted to ward

7.3 Date of most recent exposure

7.4 Name of healthcare facility attended

**Antibiotic exposure**

8.1 Systemic antibiotic use in the last 3 months

8.2 Indication

(1=UTI, 2=LRTI, 3=URTI, 4=SSTI, 5=diarrhoea, 6=other)

8.3 Duration of treatment (in days)

8.4 Class of antibiotic #1

8.5 Class of antibiotic #2

(1=BL, 2=BL/BLI, 3=cephalosporin, 4=quinolone, 5=macrolide, 6=carbapenem, 7=other)
**Microbiology within previous 6 months**

9.1 Specimen 
+ Specimen = __________________________
   - (1=blood, 2=urine, 3=skin/wound, 4=other: specify_______________________________)

9.2 Organism 
+ Organism = __________________________
   - (1=enterobacteriaceae, 2=C.difficile, 3=Staphylococcus aureus, 4=other:__________________________)

9.3 Susceptibility 
+ Susceptibility = __________________________
   - (1=WT, 2=ceftriaxone-resistant, 3=quinolone-resistant, 4=ceftriaxone plus quinolone-resistant, 5=MRSA)

9.4 Previous C.difficile diarrhoea 
+ Previous C.difficile diarrhoea = __________________________

9.5 If yes, please include date 
   - Date = __________/________/________

**Functional Status**

10.1 Mobility status 
+ Mobility status = __________________________
   - (1=bedbound, 2=chair-bound, 3=walks with assistance, 4=walks independently)

10.2 Katz Index of IADL score 
+ Katz Index of IADL score = __________________________

10.3 Clinical diagnosis of dementia 
+ Clinical diagnosis of dementia = __________________________

10.4 Three-word recall score 
+ Three-word recall score = __________________________

**Concomitant medication**

11.1 Currently using systemic corticosteroids 
+ Currently using systemic corticosteroids = __________________________

11.2 Currently using proton pump inhibitor 
+ Currently using proton pump inhibitor = __________________________

**Co-morbidities**

12.1 Diabetes Mellitus 
+ Diabetes Mellitus = __________________________

12.2 Hypertension 
+ Hypertension = __________________________

12.3 COPD 
+ COPD = __________________________

12.4 Malignancy 
+ Malignancy = __________________________
12.5 HIV

12.6 Tuberculosis

12.7 Heart failure

12.8 Other

(specify________________)

12.9 Modified Charlson co-morbidity index score

12.10 Current pressure sore or skin ulceration

Sample collection

14.1 Stool/rectal sample collected

14.2 Date

14.3 Skin swabs collected

14.4 Date

Data entered by_______

Data captured by________

Date ........../ ........../ ..........

Date ........../ ........../ ..........
9. The International Journal of Infectious Diseases (IJID) instructions to authors

Instructions to authors: The International Journal of Infectious Diseases (IJID) is published monthly by the International Society for Infectious Diseases.

IJID is a peer-reviewed, open access journal and publishes position papers, original clinical and laboratory-based research, together with reports of clinical trials, reviews, exceptional case reports. The interest areas of the IJID are epidemiology, clinical diagnosis, treatment, and control of infectious diseases with particular emphasis placed on under-resourced countries. The IJID does not publish veterinary studies and studies based on animal models alone.

Manuscript types

Original articles on infectious disease topics of broad interest. We particularly welcome papers that discuss epidemiological aspects of international health, clinical reports, clinical trials and reports of laboratory investigations. Original articles should not exceed 3500 words in length. The word count is from the introduction through to the end of the conclusion/discussion and does not include abstract, tables, figures, acknowledgements or reference list.

Reviews on topics of importance to readers in diverse geographic areas. These should be comprehensive and fully referenced.

Article requirements: Word count for the main part of the manuscript from introduction to conclusion/discussion: 2,500 to max of 4000 words. One or two figures/tables, a brief abstract, an introduction, a conclusion, and no more than 30 references.

Perspectives are papers that advance a hypothesis or represent an opinion relating to a topic of current interest or importance. They should be fully referenced, and should not exceed 2000 words in length.

Correspondence relating to papers recently published in the Journal, or containing brief reports of unusual or preliminary findings. Maximum length 400 words, one table or figure and a maximum of 10 references.

Case Reports must be carefully documented and must be of importance because they illustrate or describe unusual features or have important therapeutic implications. Maximum length 1200 words and a maximum of 1 table or figure. Case reports require an abstract, but this does not need to be a structured abstract and should include no more than 15 references.

Short Communications brief reports of unusual or preliminary findings. Maximum length 800 words, two tables or figures and a maximum of 10 references.

Medical Imagery: We would like to invite submission of high-quality, interesting and instructive images (such as clinical and other photographs, figures or diagrams, photomicrographs, or diagnostic imaging) suitable for the general readership of IJID. These should include no more than 200 words of explanatory text, and under 5 references. It is necessary to have appropriate permissions from subjects for an identifiable clinical image to be published.

Essential title page information

• Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• Author names and affiliations. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors’ affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. Ensure that the e-mail address is given and that contact details are kept up to date by the
corresponding author.

- **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a ‘Present address’ (or ‘Permanent address’) may be indicated as a footnote to that author’s name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

**Covering letter**

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